

# Falls and Cognition in Older Persons

Fundamentals, Assessment  
and Therapeutic Options

Manuel Montero-Odasso  
Richard Camicioli  
*Editors*



Springer

---

# Falls and Cognition in Older Persons

---

Manuel Montero-Odasso  
Richard Camicioli  
Editors

# Falls and Cognition in Older Persons

Fundamentals, Assessment  
and Therapeutic Options

*Editors*

Manuel Montero-Odasso  
Division of Geriatric Medicine  
University of Western Ontario  
London, ON  
Canada

Richard Camicioli  
Division of Neurology  
University of Alberta  
Edmonton, AB  
Canada

ISBN 978-3-030-24232-9      ISBN 978-3-030-24233-6 (eBook)  
<https://doi.org/10.1007/978-3-030-24233-6>

© Springer Nature Switzerland AG 2020

Chapter 2 was created within the capacity of an US governmental employment. US copyright protection does not apply.

All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG  
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland



*To my wife Denise, and our children Violet and Max, who have the virtue of making the bad moments vanish, and the good moments shine.*

*Manuel Montero-Odasso*

*Dedicated to my wife Wendy and our children, Amy and Emma, who provide meaning to life and work and support my reading, writing, and exercise habits.*

*Richard Camicioli*

---

## Foreword

Falls represent one of the most common, morbid, and costly threats to independence and quality of life in older adults. They are strongly associated with fractures, dementia, functional decline, mortality, and excess health care expenditures. Despite their high prevalence, adverse consequences, and extensive study over many years, there are still many unanswered questions regarding their causes and prevention. Why are falls so common in older age, especially in people with cognitive problems? Why do older people walk so slowly, particularly when they are talking to others, using a cell-phone, or negotiating an intersection? And what, if anything, can be done to overcome these ubiquitous age-related changes in mobility and thereby prevent falls? These questions and many others are the subject of this authoritative book, edited by two leading experts in the fields of cognitive neurology and geriatric medicine. The understanding of the causes and prevention of falls cannot be achieved by any one scientific discipline, but requires multidisciplinary expertise from the fields of geriatrics, neurology, kinesiology, physical medicine, nursing, engineering, epidemiology, and many others. Remarkably, Drs. Montero-Odasso and Camicioli have assembled an outstanding group of international authors who bring the most current, evidence-based information and professional experience from multiple disciplines to this comprehensive and scholarly work.

This book is unique in many ways. As its title indicates, the book emphasizes the importance of the brain and cognitive processes in the control of mobility. Prior to this writing, the critical role of the central nervous system (CNS) in causing and counteracting falls received relatively little attention in the medical literature. A 2014 National Institute on Aging/Gerontological Society of America workshop emphasized the understudied role of the CNS in mobility impairment. Although there are many disease-, drug-, and environmentally related causes of mobility decline in older age, these generally build upon underlying age-related structural and functional changes in the brain. One conceptual theme resonating throughout the book is that executive cognitive processes are essential for normal gait and balance. Executive functions, emanating largely from the prefrontal cortex, include attention, planning, organizing, and multitasking. A decline in these executive functions is associated with the slowing of gait speed and associated falls that so commonly occur in older adults. Dual-task protocols, such as walking while talking or counting, are highlighted in the text as novel experimental paradigms to probe abnormalities in executive control and quantify responses to various interventions.

Another unique feature of this book is its welcome departure from the classic descriptions of falls as “accidental,” “extrinsic,” or “mechanical,” which imply that they are due to unavoidable external environmental hazards or stressors, rather than pathological conditions intrinsic to the faller him- or herself. In fact, falls are often due to the dynamic interaction of “intrinsic” and “extrinsic” factors, which makes it difficult for the faller to adapt to environmental challenges. Therefore, interventions must focus not only on changing the environment, but also on improving the adaptive capacity of the older individual.

The later sections of the book provide an informative review of promising, innovative interventions to prevent falls that are based on recent discoveries of brain structures and functions that control mobility. These include physical, cognitive, and combined exercise programs; virtual reality training; pharmacologic agents; and noninvasive electrical and magnetic brain stimulation. Many of these interventions target frontal lobe executive deficits, lending further support to the book’s conceptual framework linking abnormal executive functions to mobility impairments and falls.

This book should be required reading for anyone studying or treating falls in older adults. It should also inspire future research in the field. With the recent development of multimodal imaging techniques, biomarkers of nervous system function, and genetic tools to map and manipulate neural pathways responsible for gait, additional interventions to prevent falls are on the horizon. As this valuable textbook illustrates, by better understanding and treating the cognitive processes that control mobility, the syndrome of falling in old age may soon become a preventable condition.

Lewis Lipsitz, MSc, MD, FGSA  
Professor of Medicine, Harvard Medical School  
Chief, Division of Gerontology, Beth Israel Deaconess Medical Center  
Director, Hinda and Arthur Marcus Institute for Aging Research & Chief  
Academic Officer  
Irving and Edyth S. Usen and Family Chair in Medical Research  
Boston, MA, USA

---

## A Personal Note

“By bringing his body up into a vertical position, modifying his hands in one way and his feet in another, and by improving his brain still further and using it as hard as he could, he stood a chance of success.”

Desmond Morris

In *The Naked Ape: A Zoologist's Study of the Human Animal*. McGraw-Hill, 1967, p. 25.

In the early 1990s, my first mentor in Geriatric Medicine, Professor Roberto Kaplan, encouraged me to read Desmond Morris' book *The Naked Ape* to quench my deep curiosity about the complexity of balance and gait control in humans from an “evolutionary” perspective.

I was avidly reading it when I experienced a “eureka” moment in chapter 1 as I learnt that bipedalism, the human ability to walk habitually on two feet, played an essential role in enabling the process of encephalization, the expansion of human brain size at the expense of the frontal lobes. This moment also planted a thought in my mind about the “gait and brain” connection. That evolved, over the years, into the idea that human bipedalism must have relied on the encephalization process to further adjust motor and dynamic balance control.

Desmond Morris' book provided me with a phylogenetic and evolutionary rationale for my clinical observation that the functional decline associated with aging originates from impairments of two sophisticated and complex human achievements: gait and cognition.

Over the next 25 years, it has become clearer that the decline in mobility and cognition seen in aging are, in fact, two faces of the same coin, two highly interrelated and quintessential manifestations of human aging.

Manuel Montero-Odasso, MD, PhD, FRCPC, AGSF, FGSA

My early interest in aging was driven as much by thinking about science fiction as science. Aging is a fundamental biological process that motivated me to pay attention to issues in Geriatric Medicine and ultimately focus on Geriatric Neurology as more “tractable” than all of medicine. The study of falls, which represent a critical systems failure, brings medicine and neurology and systems science together and motivates this book.

Richard Camicioli, MD, FRCPC

---

## Preface

Despite the enormous efforts of researchers and clinicians to understand the pathophysiology of falls in older adults and establish preventive treatments, there is still a significant gap in our understanding and treating of this challenging syndrome, particularly when we focus on cognitively impaired older adults. Falls in older adults are a very common yet complex phenomena, being the fifth leading cause of death and a main cause of disability in our aging world population. Importantly, falls in the cognitively impaired double the prevalence in the cognitively normal, affecting up to 60% of them, and increasing their risk for injuries.

The past decade has witnessed an explosion of new knowledge about the role of cognitive processes in falls mechanisms. This was also accompanied by clinical trials assessing the effect of improving cognition to prevent falls and related injuries using pharmacological and non-pharmacological approaches. Unfortunately, this revolution in emerging interventions left a gap between researchers at academic centers, where the new data had been generated, and the practitioners who care for cognitively impaired patients with falls. Most advances are published in specialty journals of Geriatric Medicine, Neurology, and Rehabilitation and may not reach practitioners. Little of this new knowledge has translated into clinical practice.

The main aim of this book is to provide an overview of the emerging research in falls and cognition and to provide practical tools for fall prevention in cognitively impaired populations. We have drawn in all the disciplines that consider falls in older adults with cognitive problems. We have purposely designed our book to present a comprehensive and state-of-the-art update that covers the pathophysiology, epidemiology, and clinical presentation of falls in cognitively impaired older adults. Existing books on fall prevention focus on global approaches and only tangentially address the cognitive component of falls, without addressing special populations with cognitive impairments. We have tried to provide practical evidence-based strategies for the assessment, approach, and management of falls in cognitively impaired populations. The role of falls prevention and the emerging concept of “targeting cognition to improve mobility and reduce falls” are also discussed and current evidence appraised.

This book is composed of five major sections that were tasked to an outstanding international cadre of experts who are leading research and clinical approaches in falls in the cognitively impaired. These sections follow a reductionist and logical order but they do not necessarily need to be read sequentially. Part I serves as the

foundation. Here, experts in the field summarize the fundamentals of the cognition and mobility interaction in older adults, and the epidemiology of falls in the cognitively impaired. Part II examines clinical tools available and how to assess fall risk in the cognitively impaired individuals. The role of assistive devices, polypharmacy, and neuroimaging is also reviewed. Part III focuses on falls and consequences in special hosts and environments including mild cognitive impairment, Alzheimer's disease, Parkinson's disease and related disorders, and addressing settings such as the community, acute hospitals, and nursing homes. Part IV evaluates the role of prevention, the gaps in current guidelines for falls assessment and management, and looks at the emerging treatments and novel modalities to manage falls in the cognitively impaired. Importantly, we also highlight the emerging approach of improving cognition to improve mobility and reduce falls. Lastly, Part V is a single chapter dedicated to future directions, exploring the role of new technologies and wearable devices to monitor mobility and falls.

We believe that by including a trans-disciplinary perspective from Geriatric Medicine, Neurology, Rehabilitation and Physiotherapy Medicine, Cognitive Neurology, Movement Disorders, and Public Health, this book provides a practical and useful resource with wide applicability in falls assessment and prevention.

London, ON, Canada

Manuel Montero-Odasso, MD, PhD, FRCPC, AGSF, FGSA

Edmonton, AB, Canada

Richard Camicioli, MD, FRCPC

---

## Acknowledgments

In addition to all the expert authors who have shared their thoughts, hard work, and time to make this book a reality, we want to recognize other experts, clinicians, and researchers, who have mentored us directly or indirectly and influenced our writing and our development of ideas and philosophies about these geriatric giants: falls and cognitive impairments. They deserve our recognition and gratitude. These individuals include Roberto Kaplan, Howard Bergman, Howard Chertkow, Gary Naglie, David Hogan, Ken Rockwood, Lewis Lipsitz, Jonathan Bean, David Krebs (†), Neil Alexander, Jennie Wells, Michael Borrie, Stephen Lord, Jacqui Close, Sue Lord, Lynn Rochester, Rose Anne Kenny, Tahir Masud, John Starr (†), James Williamson (†), Bernard Isaacs (†), Brian Maki, Jeffrey Kaye, Jay Nutt, and many others. As always, our families are the foundation of our lives and we are ever grateful for their support. Many thanks to our editorial assistants Prakash Marudhu and Nadina Persaud, and to Dr Yanina Sarquis-Adamson for her help in editing and proofing final versions of the chapters. Errors that remain in the book despite all the help offered by our friends, colleagues, and family are, of course, ours own. Most of all, we are indebted to our patients from whom we learn every day the humbleness of Medicine. We hope this book can contribute to improve the care of older adults with mobility and cognitive impairments.



---

# Contents

## Part I Fundamentals

<b>1 Falls as a Manifestation of Brain Failure: Gait, Cognition, and the Neurobiology of Falls . . . . .</b>	<b>3</b>
Manuel Montero-Odasso and Richard Camicioli	
<b>2 Dismobility in Aging and the Role of Cognition and Health Consequences of Reduced Mobility. . . . .</b>	<b>21</b>
Qu Tian and Stephanie A. Studenski	
<b>3 Epidemiology and Falls Risk Factors in Cognitively Impaired Older Adults . . . . .</b>	<b>35</b>
Stephanie A. Bridenbaugh and Reto W. Kressig	
<b>4 Depression, Fear of Falling, Cognition and Falls. . . . .</b>	<b>49</b>
Ryota Sakurai and Yoshiro Okubo	
<b>5 Frailty, Cognition, and Falls. . . . .</b>	<b>67</b>
Lindsay M. K. Wallace, Olga Theou, and Kenneth Rockwood	

## Part II Assessments

<b>6 Comprehensive Falls Assessment: Cognitive Impairment Is a Matter to Consider. . . . .</b>	<b>87</b>
Olivier Beauchet and Manuel Montero-Odasso	
<b>7 Gait Variability and Fall Risk in Older Adults: The Role of Cognitive Function. . . . .</b>	<b>107</b>
Frederico Pieruccini-Faria, Manuel Montero-Odasso, and Jeffrey M. Hausdorff	
<b>8 Assistive Devices, Falls, and Cognitive Aspects . . . . .</b>	<b>139</b>
Susan W. Hunter	
<b>9 Medication Use and Falls in People with Cognitive Impairment. Assessment and Management Strategies . . . . .</b>	<b>151</b>
Allen R. Huang and Louise Mallet	
<b>10 Neurobiology of Falls: Neuroimaging Assessment. . . . .</b>	<b>165</b>
Andrea L. Rosso, Neelesh K. Nadkarni, and Caterina Rosano	

### Part III Special Patients and Settings

- 11 Falls in Parkinson's Disease and Lewy Body Dementia . . . . . 191**  
Stephen Joza, Richard Camicioli, and Fang Ba
- 12 Falls in Older Adults with MCI and Alzheimer's Disease. . . . . 211**  
Gilles Allali and Joe Verghese
- 13 Delirium, Restraint Use and Falls . . . . . 229**  
Pieter Heeren, Elke Detroyer, and Koen Milisen
- 14 Approaches for Falls Prevention in  
Hospitals and Nursing Home Settings. . . . . 245**  
Jesse Zanker and Gustavo Duque

### Part IV Prevention and Interventions

- 15 Evidence, Recommendations, and Current  
Gaps in Guidelines for Fall Prevention and Treatments . . . . . 263**  
Susan W. Hunter and Mark Speechley
- 16 Exercise to Prevent Falls in Older Adults with  
Cognitive Impairment. . . . . 273**  
Teresa Liu-Ambrose, Jennifer C. Davis, and Chun Liang Hsu
- 17 Cognitive Training and Mobility: Implications for  
Falls Prevention. . . . . 289**  
Karen Z. H. Li and L. Bherer
- 18 Virtual Reality Training as an Intervention to Reduce Falls . . . . . 309**  
Anat Mirelman, Inbal Maidan, Shirley Shema Shiratzky,  
and Jeffrey M. Hausdorff
- 19 Cognitive Enhancers as a Means to Reduce Falls in Older Adults . . . 323**  
Nicolaas I. Bohnen and Martijn L. T. M. Müller
- 20 Dual-Task Training in Cognitively Impaired and Intact Older  
Populations to Reduce Fall Risk: Evidence from Previous  
Intervention Trials by Using a Systematic Review Approach. . . . . 343**  
Klaus Hauer, Phoebe Ullrich, and Christian Werner
- 21 Noninvasive Brain Stimulation to Reduce Falls in Older Adults . . . . 373**  
Brad Manor, On-Yee Lo, Junhong Zhou, Prabhjot Dhami,  
and Faranak Farzan

### Part V Future Directions and Conclusions

- 22 Engineering Human Gait and the Potential Role of Wearable  
Sensors to Monitor Falls. . . . . 401**  
Ervin Sejdić, Alan Godfrey, William McIlroy,  
and Manuel Montero-Odasso

- Index. . . . . 427**

---

## Author Biography

**Manuel Montero-Odasso, MD, PhD, FRCPC, AGSF, FGSA** completed his undergraduate Medical Degree (Summa Cum Laude) and his Doctorate in Medicine and Gerontology at the University of Buenos Aires, Argentina. His postgraduate medical training included residencies in Internal Medicine and Geriatric Medicine. He completed a postdoctoral clinical and research fellowship at McGill University, Canada, after which he obtained certification in Internal Medicine and Geriatric Medicine by the Royal College of Physician and Surgeons, Canada. He is currently Professor in the Departments of Medicine, and Epidemiology and Biostatistics at the University of Western Ontario, London, Canada. He is the director of the “Gait and Brain Lab” at Parkwood Institute, London, Ontario, where he established a successful research program in “Gait and Brain Health” while remaining an active geriatrician. He focuses on gait performance research combined with neuroimaging as a methodology for the early detection and future prevention of the development of frailty, falls, and dementia in older adults. His clinical trials have applied the novel approach of “improving cognition to improve mobility” by using pharmacological and non-pharmacological interventions, such as physical exercise and cognitive training and noninvasive brain stimulation. He is team leader and member of the executive board of the Canadian Consortium on Neurodegeneration in Aging (CCNA), Canada’s dementia research strategy and Team co-leader in the Ontario Neurodegenerative Research Initiative.

**Richard Camicioli, MD, FRCPC** completed his undergraduate education in Engineering Chemistry at Queen’s University in Kingston, Ontario. He trained in Medicinal Chemistry at McGill University where he completed his medical education. After completing a neurology residency at McGill, he obtained postgraduate research training in Geriatric Neurology and in Movement Disorders at Oregon Health and Sciences University and the Portland VA Medical Center in Portland, Oregon. He then assumed a faculty position as Assistant Professor at Oregon Health and Sciences University until 2000 when he moved to the University of Alberta, initially as an Associate Professor in the Department of Medicine (Neurology Division). He is currently Professor and Director of the Cognitive Neurology Program and an attending physician in the Movement Disorder Program. His major research interests relate to bio-fluid, gait, and neuro-imaging biomarkers associated with cognition and functional decline in aging and in patients with movement disorders. He directs the Canadian Consortium on Neuro-degeneration of Aging (CCNA) Lewy Body Team.

---

## Contributors

**Gilles Allali** Department of Neurology, Division of Cognitive & Motor Aging, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

Department of Clinical Neurosciences, Geneva University Hospitals and University of Geneva, Geneva, Switzerland

**Fang Ba** Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

**Olivier Beauchet** Faculty of Medicine, McGill University, Montreal, QC, Canada  
Department of Medicine, Division of Geriatric Medicine, Sir Mortimer B. Davis – Jewish General Hospital and Lady Davis Institute for Medical Research, McGill University, Montreal, QC, Canada

**L. Bherer** PERFORM Centre, Concordia University, Montreal, QC, Canada  
Department of Medicine, Université de Montréal, Montreal, QC, Canada  
Centre de Recherche de l’Institut Universitaire de Gériatrie de Montréal, Montreal, QC, Canada  
Research Center, Montreal Heart Institute, Montreal, QC, Canada

**Nicolaas I. Bohnen** Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Department of Neurology, University of Michigan, Ann Arbor, MI, USA  
Veterans Administration Ann Arbor Healthcare System, Ann Arbor, MI, USA  
Morris K. Udall Center of Excellence for Parkinson’s Disease Research, University of Michigan, Ann Arbor, MI, USA  
Functional Neuroimaging, Cognitive and Mobility Laboratory, University of Michigan, Domino’s Farms, Ann Arbor, MI, USA

**Stephanie A. Bridenbaugh** University Department of Geriatric Medicine FELIX PLATTER, Basel, Switzerland

**Richard Camicioli** Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

**Jennifer C. Davis** Center for Hip Health and Mobility, Vancouver, BC, Canada

Faculty of Management, University of British Columbia Okanagan, Kelowna, BC, Canada

**Elke Detroyer** Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, Leuven, Belgium

Department of Geriatric Medicine, University Hospitals Leuven, Leuven, Belgium

**Prabhjot Dhami** Centre for Addiction and Mental Health, Toronto, ON, Canada

Institute of Medical Science, Faculty of Medicine, University of Toronto, Medical Sciences Building, 1 King's College Circle, Toronto, ON, Canada

**Gustavo Duque** Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St. Albans, VIC, Australia

Department of Medicine-Western Health, Melbourne Medical School, The University of Melbourne, St. Albans, VIC, Australia

Department of Geriatric Medicine, Western Health, St. Albans, VIC, Australia

**Faranak Farzan** Centre for Addiction and Mental Health, Toronto, ON, Canada

Institute of Medical Science, Faculty of Medicine, University of Toronto, Medical Sciences Building, 1 King's College Circle, Toronto, ON, Canada

School of Mechatronic Systems Engineering, Simon Fraser University, Surrey, BC, Canada

Department of Psychiatry, University of Toronto, Toronto, ON, Canada

**Alan Godfrey** Department of Computer and Information Sciences, Northumbria University, Newcastle upon Tyne, UK

**Klaus Hauer** Agaplesion Bethanien-Hospital/Geriatric Center at the Heidelberg University, Heidelberg, Germany

**Jeffrey M. Hausdorff** Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv-Yafo, Israel

Department of Physical Therapy, Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL, USA

**Pieter Heeren** Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, Leuven, Belgium

Department of Geriatric Medicine, University Hospitals Leuven, Leuven, Belgium  
Research Foundation Flanders, Brussels, Belgium

**Chun Liang Hsu** Aging, Mobility, and Cognitive Neuroscience Lab, University of British Columbia, Vancouver, BC, Canada

Department of Physical Therapy, University of British Columbia, Vancouver, BC, Canada

Djavad Mowafaghian Center for Brain Health, University of British Columbia, Vancouver, BC, Canada

Center for Hip Health and Mobility, Vancouver, BC, Canada

**Allen R. Huang** Division of Geriatric Medicine, Department of Medicine, University of Ottawa & The Ottawa Hospital, Ottawa, ON, Canada

**Susan W. Hunter** School of Physical Therapy, University of Western Ontario, London, ON, Canada

**Stephen Joza** Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

**Reto W. Kressig** University Department of Geriatric Medicine FELIX PLATTER, Basel, Switzerland

**Karen Z. H. Li** Department of Psychology, Concordia University, Montreal, QC, Canada

Centre for Research in Human Development, Concordia University, Montreal, QC, Canada

PERFORM Centre, Concordia University, Montreal, QC, Canada

**Teresa Liu-Ambrose** Aging, Mobility, and Cognitive Neuroscience Lab, University of British Columbia, Vancouver, BC, Canada

Department of Physical Therapy, University of British Columbia, Vancouver, BC, Canada

Djavad Mowafaghian Center for Brain Health, University of British Columbia, Vancouver, BC, Canada

Center for Hip Health and Mobility, Vancouver, BC, Canada

**On-Yee Lo** Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

**Inbal Maidan** Laboratory for Early Markers Of Neurodegeneration (LEMON), Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel

Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel

Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

**Louise Mallet** Faculty of Pharmacy, Université de Montréal, and Clinical Pharmacist in Geriatrics, McGill University Health Centre, Montreal, QC, Canada

**Brad Manor** Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

**William McIlroy** Department of Kinesiology, University of Waterloo, Waterloo, ON, Canada

**Koen Milisen** Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, Leuven, Belgium

Department of Geriatric Medicine, University Hospitals Leuven, Leuven, Belgium

**Anat Mirelman** Laboratory for Early Markers Of Neurodegeneration (LEMON), Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel

Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel

Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

**Manuel Montero-Odasso** Departments of Medicine (Geriatric Medicine), and Epidemiology and Biostatistics, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada

Gait and Brain Lab, Parkwood Institute, Lawson Health Research Institute, London, ON, Canada

**Martijn L. T. M. Müller** Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Morris K. Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor, MI, USA

**Neelesh K. Nadkarni** University of Pittsburgh School of Medicine, Department of Medicine (Division of Geriatric Medicine), Department of Neurology, and the Alzheimer's Disease Research Center, Pittsburgh, PA, USA

**Yoshiro Okubo** Falls, Balance and Injury Research Centre, Neuroscience Research Australia, Randwick, NSW, Australia

UNSW Sydney, Sydney, NSW, Australia

**Frederico Pieruccini-Faria** Department of Medicine, Division of Geriatric Medicine, University of Western Ontario, London, ON, Canada

Gait and Brain Lab, Parkwood Institute and Lawson Health Research Institute, London, ON, Canada

**Kenneth Rockwood** Department of Medicine, Dalhousie University, Halifax, NS, Canada

Geriatric Medicine Research Unit, Centre for Health Care of the Elderly, Nova Scotia Health Authority, Halifax, NS, Canada

**Caterina Rosano** University of Pittsburgh Graduate School of Public Health, Department of Epidemiology, Pittsburgh, PA, USA

**Andrea L. Rosso** University of Pittsburgh Graduate School of Public Health, Department of Epidemiology, Pittsburgh, PA, USA

**Ryota Sakurai** Research Team for Social Participation and Community Health, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

**Ervin Sejdić** Department of Electrical and Computer Engineering, Swanson School of Engineering, Department of Bioengineering, Swanson School of Engineering, Department of Biomedical Informatics, School of Medicine, Intelligent Systems Program, School of Computing and Information, University of Pittsburgh, Pittsburgh, PA, USA

**Shirley Shema Shiratzky** Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel

**Mark Speechley** Department of Epidemiology & Biostatistics, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada

**Stephanie A. Studenski** Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, Baltimore, MD, USA

University of Pittsburgh, Pittsburgh, PA, USA

**Olga Theou** Department of Medicine, Dalhousie University, Halifax, NS, Canada  
Geriatric Medicine Research Unit, Centre for Health Care of the Elderly, Nova Scotia Health Authority, Halifax, NS, Canada

**Qu Tian** Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging, Baltimore, MD, USA

**Phoebe Ullrich** Agaplesion Bethanien-Hospital/Geriatric Center at the Heidelberg University, Heidelberg, Germany

**Joe Verghese** Department of Neurology, Division of Cognitive & Motor Aging, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

**Lindsay M. K. Wallace** Faculty of Graduate Studies, Dalhousie University, Halifax, NS, Canada

Geriatric Medicine Research Unit, Centre for Health Care of the Elderly, Nova Scotia Health Authority, Halifax, NS, Canada

**Christian Werner** Agaplesion Bethanien-Hospital/Geriatric Center at the Heidelberg University, Heidelberg, Germany

**Jesse Zanker** Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St. Albans, VIC, Australia

Department of Medicine-Western Health, Melbourne Medical School, The University of Melbourne, St. Albans, VIC, Australia

Department of Geriatric Medicine, Western Health, St. Albans, VIC, Australia

**Junhong Zhou** Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife, Boston, MA, USA

Harvard Medical School, Boston, MA, USA



---

## Part I

# Fundamentals



# Falls as a Manifestation of Brain Failure: Gait, Cognition, and the Neurobiology of Falls

1

Manuel Montero-Odasso and Richard Camicioli

The probability that members of this audience will reach the age of 80 is about one and three. The probability that, of having done so, they will suffer it damaging fall is about the same. ...Can anything practical be done [to reduce falls] other than the avoidance of external hazard an unsuitable drugs?... [Can we] speculate on a possible pharmacological approach to fall prevention?

Sir Bernard Isaacs, 1978 [1]

---

## Introduction

Forty years ago, Sir Bernard Isaacs, a leading geriatrician, thinker, scholar, and initiator of many geriatric medicine principles, coined the term “geriatric giants” [2] which refers to the main chronic conditions of aging that impact on physical, mental, and social domains of older people. The geriatric giants, known as the four “Is,” are immobility, instability (falls), incontinence, and intellectual impairment. Importantly, he highlighted that the giants may come together and he linked falls (instability) with brain failure (intellectual impairment). He perceptively postulated that to attribute falls in older individuals only to muscular-articular and sensory impairments and their effect on gait and balance was overly simplistic. Rather, a failure of our sophisticated system of brain motor control plays a capital role in

---

M. Montero-Odasso (✉)

Departments of Medicine (Geriatric Medicine), and Epidemiology and Biostatistics, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada

Gait and Brain Lab, Parkwood Institute, Lawson Health Research Institute, London, ON, Canada

e-mail: [mmontero@uwo.ca](mailto:mmontero@uwo.ca)

R. Camicioli

Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

triggering falls [1, 3]. He went further by speculating that pharmacological treatments can be used to improve processing speed and attention with the goal of reducing falls in older adults. This concept in the late 1970s was quite disruptive since the “holy grail” approach to medications and falls in geriatric medicine is to reduce polypharmacy rather than to add new medications [1].

In 1976, he coined the term “brain failure” to illustrate “brain syndromes” that are accompanying, but not necessarily caused by, aging [1]. Under the “brain failure” rubric, Professor Isaacs included obvious clinical manifestations of brain impairment such as dementia, delirium, and depression; interestingly, he also suggested that the age-associated mobility decline and falls can be similarly seen as expressions of “brain failure” [4].

Refining the concept of “brain failure”, we have hypothesized that two early clinical markers of cognitive and mobility decline in older adults, executive dysfunction and slow gait, can be seen as its early manifestations. Both are strongly related to falling and may share a common underlying mechanism. Since his seminal article entitled “Brain Failure,” clinical and research evidence have established that cognitive impairment and falls are highly interrelated [5]. Indeed, at the extreme, dementia and falls often coexist in older adults; gait impairments and falls are more prevalent in dementia than in normal aging, and this prevalence increases with the severity of cognitive impairment [6]. Data are accumulating that mild and selective cognitive changes prior to the development of dementia are important manifestations of brain failure and falls.

Falling, a common geriatric syndrome affecting about a third of older adults each year, is a major cause of morbidity, with higher prevalence in those with moderate to severe cognitive impairment and an annual incidence of 70%, twice the rate of that in cognitively normal older adults [7]. The consequences of falls in this group are serious; fallers with cognitive problems are approximately five times more likely to be admitted to institutional care than cognitively impaired people who do not fall [8]. They are also at high risk of major fall-related injuries, including fractures, head injuries, and mortality. In addition to indirect costs and caregiver burden, the direct costs of emergency, acute, rehabilitation, and long-term care due to falls are substantial and are currently a challenge for healthcare systems’ sustainability. Changes in behavior (such as increased isolation and restricting mobility) also can have downstream health consequences [9].

As currently understood, cognition is a complex construct comprising several domains related to distinct brain networks and areas. While the precise mechanisms underlying increased fall risk in cognitively impaired older adults are not completely deciphered, it seems clear that impaired attentional resource allocation significantly compromises postural and gait stability [10]. Specifically, executive function, a set of cognitive processes that includes attention, inhibitory control, switching attention, working memory, and cognitive flexibility, is essential for normal walking. Just in the last few years, it was demonstrated that executive dysfunction is associated with increased fall risk, even in those “labeled” as cognitively normal [11]. Such findings challenge our definition of clinically significant cognitive impairment. For example, even among older adults with “normal” cognition, as assessed using screening tests such as the Mini-Mental State Examination, low performance in executive function is prospectively associated with falls [12].

Many early prospective cohort studies of falling in older adults systematically excluded those with moderate or severe cognitive impairment, which limited our ability to evaluate fall risk across the full cognitive spectrum. Consequently, until recently, falls, cognitive impairment, and dementia were assessed in research studies separately which has led to a gap in our understanding of the cognitive-motor interactions that affect the pathways to future falls and fall-related disability. This gap may also explain why cognition has received little attention in fall prevention strategies. Mounting evidence reveals these two geriatric syndromes, falls and cognitive impairment, are interrelated and associated with aging [5].

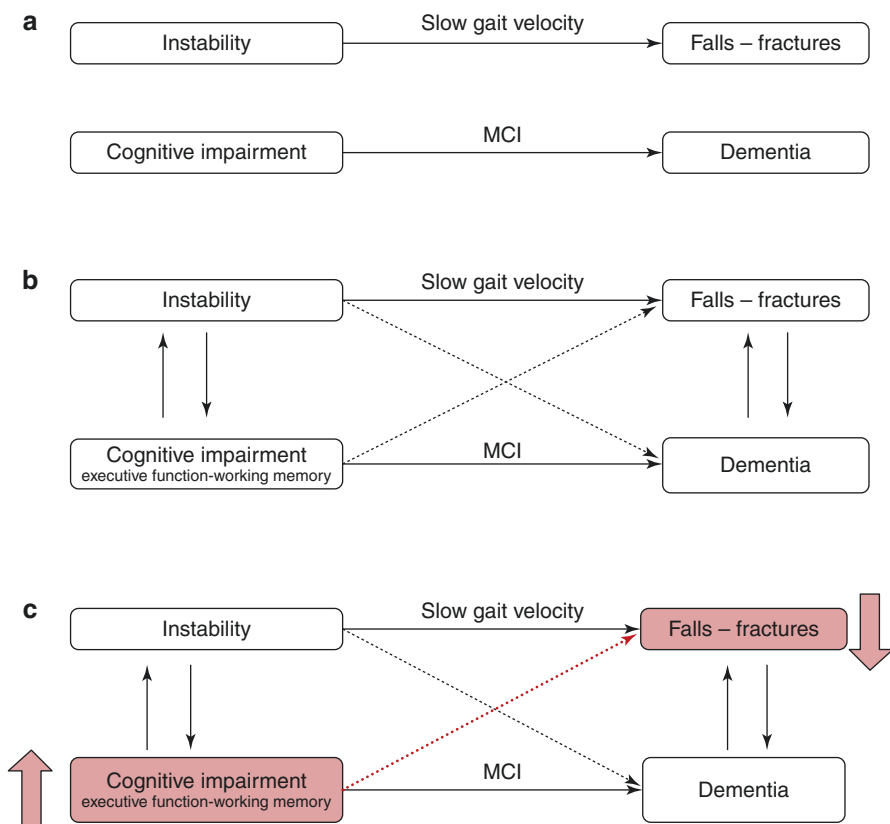
---

## Cognition, Gait, and Falls in Aging

Although walking was long considered a primarily automatic motor task, it is now accepted that this view was too simplistic [13]. Walking in the real world requires paying attention to various changing environmental features and shifting attention to avoid trips and slips and quickly recovering from inevitable postural perturbations to regain a stable base of support. Therefore, it is not surprising that deficits in attention and executive function processes are independently associated with risk of postural instability, impairment in activities of daily living, and future falls [11]. Previous systematic reviews have shown a relationship between executive dysfunction and falls, and a meta-analysis of 27 prospective cohort studies found that executive dysfunction doubled the risk for future falls and increased the risk of serious injury by 40% in community-dwelling older adults [14].

Older adults with mild cognitive impairment (MCI), a transitional state between normal aging and early dementia, have a higher prevalence of gait impairments and higher risk of falling compared to cognitively normal older adults [15–18]. Thus, MCI is a population at risk, not only for future dementia but also for falls, and should perhaps be specifically targeted for interventions to reduce fall risk. One specific early change in gait performance seen among cognitively impaired older adults is a decrease in gait speed [6]. Quantitative spatiotemporal gait parameters are also impaired across the entire cognitive spectrum, and gait variability, the variations in a given gait parameter from stride-to-stride, has emerged as a sensitive marker of high-level brain gait control [5, 19]. High gait variability represents gait instability and has been shown also to predict falls even before slow gait develops in older adults [20].

Mechanistically, the relationship between cognitive deficits and gait disturbances has been attributed to specific brain regions such as the prefronto-parietal and cingulate cortical areas and striatal hippocampal networks. These areas can be affected by neurodegeneration (amyloid and tau pathology [21]), brain small vessels disease, and aging as demonstrated by brain imaging studies [22]. Figure 1.1 shows a conceptual framework proposed in 2010 to understand the concurrent decline of cognition and mobility in aging and how they relate to falls and dementia syndromes [5]. We have postulated that the relation between gait and cognition, as well as falls and dementia, is bidirectional [5, 23]. Until recently, falls and dementia were studied and assessed as distinct geriatric syndromes (Fig. 1.1a). This has led to a gap in our



**Fig. 1.1** Parallel declines in gait and cognition with aging and risk of falls. (a) Traditional view: gait and cognitive function deteriorate with aging, yielding two geriatric entities: falls and dementia. (b) Emerging view (dashed arrows): low cognition also predicts mobility decline and falls, and mobility decline and slow gait also predict cognitive deterioration. (c) Potential therapeutic view: (in red and red dashed arrow) improving cognition could reduce falls and fractures. *MCI* mild cognitive impairment. (Adapted from Montero-Odasso et al. [5])

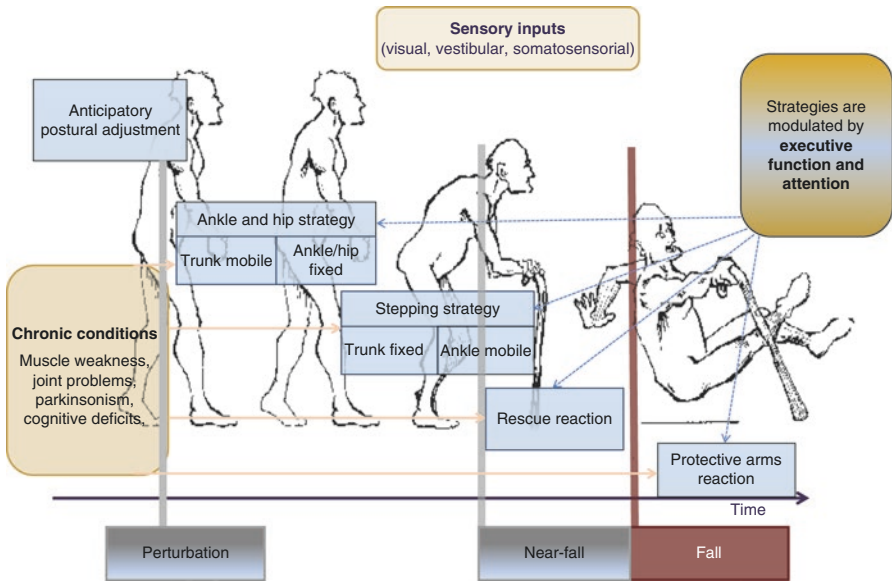
understanding of the cognitive-motor interactions that affect the pathways to future falls and falls-related disability in older adults. This gap may also explain why cognition has received little attention with regard to intervention strategies for falls prevention. New evidence supports that these two geriatric syndromes are interrelated outcomes associated with aging (Fig. 1.1b). Importantly, this conceptual framework opened the field to include the enhancement of cognition as part of the armamentarium of fall prevention and management of falls (Fig. 1.1c).

## Cognitive Aspects of the Pathophysiology of Falls

The human upright position is naturally unstable with a narrow base of support and a high center of body mass. To maintain this delicate equilibrium while walking or standing, the human body uses harmonious modulation and coordination of trunk,

hip, and ankle flexibility. This equilibrium is challenged by impairments such as muscle weakness, joint problems, motor slowness, or poor coordination, among other impairments. These challenges increase the risk of falling under physiological perturbations, like body sway during standing or walking, or after extrinsic destabilizing factors like tripping. The rapid succession of strategies aimed at preserving postural stability after a perturbation includes first the “ankle strategy” for small perturbations and later the “hip strategy” for larger perturbations. The “ankle strategy” is a motor plan characterized by the relaxation of trunk muscles and stiffening of the ankle joint, whereas the “hip strategy” relaxes the hip muscles and stiffens the leg muscles with the head moving out of phase and the hip moving to maintain the center of body mass over the base of support [24]. When the perturbation is more severe and these strategies are insufficient, a third motor plan used to avoid falling is the “stepping strategy,” in which the ankle joint is released and the individual performs one or more steps to enlarge the base of support. Finally, if these motor acts fail to regain postural stability, the upper limbs perform rescue strategies, such as grabbing a support, or use protective reactions, such as extending the arms, to limit the traumatic consequence of falling.

In Fig. 1.2 we schematize a pathophysiological conceptual model to explain falls and the connection between trunk inflexibility (worsened by rigidity or fear of falling), instability during the “ankle strategy,” and the mechanistic link between gait and falling during the “stepping strategy.” Cognitive resources, including attention and executive functions, play a key role modulating each of these strategies [25].



**Fig. 1.2** Strategies aimed at preserving postural body stability after a single perturbation. Note the role of cognitive processes modulating the four classic strategies. (From Montero-Odasso and Speechley [23])

An adequate flow of information through visual, vestibular, and somatosensory afferents is required, shown as “sensory inputs” in Fig. 1.2, paired with attentional and executive resources to effectively adapt to the environment and to the type of perturbation by rapidly switching from one strategy to the other.

Older adults show an innate preference to maintaining posture while attempting to simultaneously perform a cognitive task by prioritizing walking over a secondary cognitive demanding task [26]. This is highlighted in situations where cognitive normal older adults adopt a “posture first” strategy to prioritize the maintenance of balance over other tasks. However, cognitively impaired older adults have limitations to enact this strategy and may regress to a “posture second” strategy by prioritizing the cognitive task over walking as it has been described in patients with Parkinson’s disease (PD) [27, 28]. Executive function also plays a role in inhibitory control, for example, by avoiding situations that may perturb balance. Lack of inhibitory control is more likely to occur in those farther along the cognitive decline spectrum and may cause a failure to accurately appraise the risk of activities that were once safe for them (e.g., older individuals climbing on ladders or roofs). This in turn would explain the higher incidence of severe injuries with increasing deterioration of executive functions, which may lead to falls from greater heights or with greater impacts. In this line of thinking, investigations have shown that while patients with dementia appear to walk slowly, they actually walk relatively faster for their motor and cognitive abilities, leading to an increased risk of falling [29]. This may reflect an inability to appropriately appraise the hazard of walking fast due to their cognitive deficits. A poignant example occurs in neurodegenerative disorders such as progressive supranuclear gaze palsy where the combination of impaired balance and impaired executive function leads to recurrent falls [30]. These multiple interactions demonstrate that improving cognitive functioning may have an essential role in the rehabilitation of gait disorders in older adults to restore “posture first” strategies.

Importantly, walking performance in real-life situations relies on cognition as demonstrated by studies using the dual-task gait paradigm, i.e., the effect on walking while performing a secondary cognitive task [5, 31]. Dual-task gait performance taxes the role of attention and executive function in the regulation of gait control [5, 10, 17, 32]. The underlying hypothesis is that two simultaneously performed tasks interfere and compete for brain cortical resources [11, 33]. Recent evidence showed that prefrontal brain activity levels while performing the dual-task gait predicted falls in high-functioning older adults [34]. Therefore, dual-task gait can act as a “brain stress test” to detect deficits of motor-gait control and fall risk, particularly in early stages of mobility decline, as shown in a recent systematic review [35]. Individuals with an overt neurological disease such as stroke, PD, or MCI and dementia have gait slowing during dual tasking [14, 16, 24]. This may explain why patients with cognitive impairments and dementia syndromes are vulnerable to dual-task challenges. Daily life activities involve many attention-demanding events that explain the high occurrence of falling while walking and performing an attentional demanding task common. Even during standing, postural sway increases when a cognitive task is performed, suggesting that constant dynamic control of postural adjustments during standing also requires certain

levels of cognitive attentional resources. The fact that central nervous system psychotropic and sedative drugs such as benzodiazepines can affect postural control, reaction times, and gait performance and increase risk of falls add to the evidence for the role of cognition in postural and gait control and falls risk.

---

## Enhancing Cognition to Improve Mobility and Prevent Falls

Trials in cognitively normal older adults have demonstrated that both multidomain (e.g., review of medications, strength and balance training, visual and hearing corrections, and environmental modifications) and single interventions (e.g., resistance exercise or progressive balance training) are successful in preventing falls. On the other hand, studies in cognitively impaired populations have been ineffective, inconsistent, or with only modest success in preventing falls [36]. Cognitively impaired older adults may be less responsive to the interventions, while having a higher risk for falls [36, 37], due to their limitations to adequately comprehend, learn, and adhere to recommendations, as well as the potentially different underlying mechanisms for falls in this population, and failure of the interventions to effectively address cognitive deficits. Regarding the latter, we have suggested that improving certain aspects of cognition in older adults may help to prevent falls [3, 5].

## Non-pharmacological Interventions

Interventions that have specifically evaluated the effects of single- and dual-task cognitive training on balance, gait, and fall risk in older adults with and without cognitive impairment and dementia are shown in Table 1.1.

### Studies in Cognitively Normal Populations

In a pilot study with 20 sedentary older adults, Verghese et al. randomly assigned them to a computerized cognitive remediation intervention or a wait-list control [38]. They found that cognitive remediation increased single- and dual-task gait speed indicating that a non-pharmacological cognitive intervention may improve gait performance, particularly during dual-task walking. The same results were obtained in a similar randomized controlled trial (RCT) in 51 community-dwelling older adults conducted by Smith-Ray et al. [39].

Combining physical exercise with dual-task training has been also evaluated to improve cognition and, in turn, mobility and gait performance. Silsupadol et al. conducted a seminal study using dual-task training among 21 older adults with balance and gait impairment showing that dual-task training with variable-priority instructions improved gait speed and benefits were sustained 12 weeks after the intervention. These results suggested that varying the focus of attention between the cognitive and motor tasks during training had more benefits than focusing on both tasks at the same time [40]. Falbo et al. replicated these results in a subsequent RCT involving 36 older adults [41]. Van het Reve et al. conducted a large, multicenter,



**Table 1.1** Non-pharmacological cognitive interventions for gait, balance, and fall risk

Study (year)	Design	Type of intervention and control	Duration	Participants	Summary of findings
<i>Cognitively normal population</i>					
You et al. (2009) [43]	RCT	Dual-task training with simultaneous motor (walking 30 m) and cognitive (memory recall) task ( $n = 8$ ) and control group ( $n = 5$ ) walked while listening to music	18 sessions, 30 min/session over 6 weeks	13 participants (age: $68.3 \pm 6.5$ years) with history of falls	Working memory under the dual-task condition improved ( $p < 0.05$ ). No significant changes in gait speed and variability were found
Silsupadol et al. (2009) [40]	RCT	Three intervention arms: Single-task training ( $n = 7$ ), dual-task training with fixed-priority instructions ( $n = 8$ ), and dual-task training with variable-priority instructions ( $n = 6$ )	12 sessions; 45 min individualized sessions, 3 times/week for 4 weeks	21 participants (aged $\geq 65$ years) with balance impairment	All groups improved balance and gait speed. Only the DT training with variable-priority instructions group demonstrated a DT training effect at the second week maintained at 12-week follow-up
Verghese et al. (2010) [38]	RCT	Computerized "Mindfit" program vs. wait-list control. Each training session included a mixture of 21 visual, auditory, and cross-modality tasks compared with wait list	24 sessions; 45–60 min/session, 3 times a week for 8 weeks	20 sedentary older adults (age: $77.4 \pm 7.0$ years) at training and wait list (age: $79.9 \pm 7.5$ years)	Gait speed and DT gait speed improved ( $p < 0.05$ and $p = 0.002$ , respectively) only in the intervention group. Processing speed improved significantly in the intervention group ( $p = 0.03$ )
Van het Reve et al. (2014) [33]	RCT	Strength-balance (SB, $n = 98$ ) or strength-balance-cognitive (SBC, $n = 84$ ) training	2 times/week; 40 min SB. SBC received cognitive training, 3 times/week for 12 weeks	182 participants (aged $\geq 65$ years) living in autonomous residences for the elderly	SBC group improved fast gait speed ( $p = 0.04$ ), dual-task gait cost ( $p = 0.03$ ), executive function (TMT B, $p = 0.001$ ), and fall rate ( $p = 0.001$ )

**Table 1.1** (continued)

Study (year)	Design	Type of intervention and control	Duration	Participants	Summary of findings
Smith-Ray et al. (2015) [39]	RCT	Computer-based cognitive training intervention ( $n = 27$ ) or measurement-only control ( $n = 24$ )	10 weeks; 3 times per week, for 60 min/session	51 participants (age: $82 \pm 6$ years) from independent living facilities	Intervention group performed better than controls on the TUG
Falbo et al. (2016) [41]		Physical single-task (ST) training ( $n = 16$ ) and physical-cognitive dual task (DT) training ( $n = 20$ )	12 weeks; 1 h twice weekly in group-based exercise classes	36 healthy active individuals (age: $72.3 \pm 5.8$ years)	Gait performance increased in both groups, but executive function increased only in DT group
<i>PD and MCI populations</i>					
Yogev-Seligmann et al. (2012) [59]	Open-label, pilot	A 4-week program of one-on-one training included walking while performing several distinct cognitive tasks	12 sessions; 3 per week for 4 weeks	7 participants with PD (age: $63.8 \pm 8.4$ years)	Gait speed and gait variability during DT significantly improved. Untrained DT also improved and was retained 1 month after the end of the training
Mirelman et al. (2011) [45]	Repeated measures design	TT with virtual obstacles. The VR simulation required obstacle negotiation while continuing to walk on the treadmill. Comparison was made to a historical control group that followed similar protocol of TT but without VR	18 sessions (3 per week for 6 weeks)	20 participants with PD (age: $67.1 \pm 6.5$ years) able to walk unassisted for at least 5 min	Dual tasking, gait speed ( $p = 0.003$ ), and stride length ( $p < 0.001$ ) were significantly improved after TTVR compared with TT alone. Dual-task gait variability decreased, and trail making test improved after TTVR training

(continued)

**Table 1.1** (continued)

Study (year)	Design	Type of intervention and control	Duration	Participants	Summary of findings
Mirelman et al. (2016) [46]	RCT	TT with non-immersive VR (participants walked on a treadmill while watching a large screen that projected a path with obstacles, multiple pathways, and distracters). Control group consisted of TT alone with no VR	18 sessions (3 per week for 6 weeks)	300 participants with normal cognition, MCI, and PD (aged 60–90 years) with a history of at least two falls	After 6 months of training, incident rate of falls was lower in TT with VR group compared with their rate of falls before the training ( $p < 0.001$ ) and compared with the TT alone group ( $p = 0.033$ )
van Ooijen et al. (2016) [47]	RCT	Inpatient adaptability treadmill (AT) training, conventional treadmill (CT) training, or usual physical therapy (UPT)	30 sessions (40 min each); 5 per week for 6 weeks	70 participants with a fall-related hip fracture (aged $\geq 65$ years)	Subgroup of participants with executive dysfunction improved walking adaptability and fear of falling
<i>Mild dementia population</i>					
Schwenk et al. (2010) [44]	RCT	Intervention group ( $n = 20$ ) underwent dual-task-based exercise training (motor, throwing or catching a ball, and cognitive, arithmetic tasks, repeating names of animals). Control group ( $n = 29$ ) performed low-intensity exercise	24 sessions over 12 weeks, 1 h twice a week	49 participants (mean age: $81.9 \pm 7.5$ years) with mild to moderate dementia (MMSE: $21.4 \pm 2.9$ )	DT training improved gait speed under dual-task ( $p < 0.001$ ), cadence ( $p = 0.007$ ), stride length ( $p = 0.001$ ), single support ( $p = 0.003$ ) under complex three-step backward calculation conditions compared with the control group

Modified and updated from Montero-Odasso and Speechley [23]

*Note:* CGI cognitive-gait intervention, DT dual-tasking, MCI mild cognitive impairment, MMSE Mini-Mental State Examination, PD Parkinson's disease, RCT randomized controlled trial, TT treadmill training, TUG Timed Up and Go, VR virtual reality

parallel group RCT in retired homes that randomly assigned 182 older adults to either strength-balance (SB) or strength-balance-cognitive (SBC) training. The SBC group had significant improvements in fast gait speed, dual-task cost, executive function, and fall rate [42]. However, a small study conducted by You et al. assigned 13 participants to either dual-task training (walking 30 min while performing a memory recall test) or control group (walking while listening to music) for 6 weeks and found that the dual-task group improved working memory but had no significant changes in gait speed or variability [43].

### Studies in Cognitively Impaired Populations

Dual-task mobility training has also been examined as a means to reduce falls in cognitively impaired populations. An RCT conducted by Schwenk et al. evaluated the efficacy of a 12-week dual-task mobility-training program in 49 participants with mild to moderate dementia. They found that the intervention group, which received progressive dual-task training, significantly improved the performance in a complex dual-task gait condition compared to the control group that received low-intensity exercises [44].

In older adults with PD, Mirelman et al. studied the effect of treadmill training enhanced with virtual reality (TTVR) in reducing falls. The TTVR intervention consisted of a screen in front of the treadmill showing a path with obstacles and targets that were designed to expose participants to real-life scenarios that could lead to falls. Results showed that TTVR improved motor-cognitive performance, assessed as dual-task gait speed, more effectively than treadmill alone [45]. The same group conducted a larger multisite RCT in a heterogeneous sample of 300 adults with normal cognition, MCI, and PD, which showed that TTVR significantly reduced fall incidence rate 6 months after the end of the training, compared with their fall incidence at baseline, and compared with the treadmill alone group [46]. A parallel group RCT conducted by van Ooijen et al. also compared treadmill training with enhanced visual stimuli against conventional treadmill training and usual physical therapy in 90 older adults rehabilitating from fall-related hip fractures [47]. They found that visually enhanced treadmill training improved walking adaptability and fear of falling only in the subgroup of participants with executive dysfunction, suggesting that for this subgroup, this modality is better than conventional treadmill training [47]. While the effects of these cognitive-based therapies on gait performance and fall risk are promising, only three of them examined falls as a primary outcome. Therefore, even though definitive trials are needed before widely recommending this approach, it appears that cognitive training with or without physical exercise can improve gait performance. Remarkably, dual-task training and treadmill training with virtual reality are feasible and promising interventions to reduce falls in cognitively impaired and PD populations, respectively.

### Pharmacological Interventions

Studies that have evaluated the effects of cognitive pharmacological interventions to improve gait and fall risk in older adults are summarized in Table 1.2. The role of cognitive enhancers for mobility outcomes and fall prevention will be addressed

**Table 1.2** Pharmacological cognitive interventions for gait and balance and fall risk

Study (year)	Study design	Type of intervention	Duration	Participants	Summary of findings
<i>Cognitively normal population</i>					
Ben-Itzhak et al. (2008) [48]	RCT, double-blind, placebo-controlled	Before and 2 h after taking 20 mg MPH or a placebo	2 h	26 participants without dementia with subjective memory complaints (age: 73.8 ± 1.2 years; mean MMSE: 27.8 ± 1.4)	MPH improved Timed Up and Go ( $p = 0.004$ ), stride time variability ( $p = 0.03$ ) and EF ( $p = 0.03$ ); effects not observed after treatment with the placebo
Shorer et al. (2013) [49]	RCT, double-blind, placebo-controlled	Before and 1.5 h after taking 10 mg MPH or a placebo	2 h	30 participants without dementia (age: 74.9 ± 5.6 years; MMSE >24)	MPH improved narrow base walking by reducing number of step errors ( $p = 0.040$ ) in single and dual tasks; effects not observed in placebo group
<i>MCI and AD populations</i>					
Assal et al. (2008) [52]	Before-after design	Galantamine mean dose of 17.8 ± 3.5 mg/day	6 months	9 participants with mild-to-moderate AD (age: 77.9 ± 2.1 years; MMSE: 26.4 ± 5.2) compared with 18 no-treatment control subjects (age: 78.1 ± 1.0 years; MMSE: 29.4 ± 0.8)	Stride time was shorter under dual tasking after treatment ( $p = 0.01$ ). There was no change in the controls
Montero-Odasso et al. (2009) [50]	Open-label study with controls	5 mg/day of donepezil for 1 month, and another 3 months with 10 mg/day. MCI group with no treatment	4 months	6 participants with mild AD (age: 79.9 ± 4.8 years; MMSE: 22.3 ± 1.2; MoCA: 15 ± 1.4) compared with 8 participants with MCI (age: 75.6 ± 6.2 years; MMSE: 27.9 ± 1.7; MoCA: 22.9 ± 1.7)	Participants with mild AD increased their single ( $p = 0.045$ ) and dual-task gait velocity ( $p = 0.047$ ) after 1 month. Stride time variability decreased (improved). Control group declined in gait speed and variability
Beauchet et al. (2011) [55]	Before-after design	Memantine mean dose of 20 mg/day, titrated in 5 mg increments over 4 weeks	4.4 to 8 months	17 participants with AD (age: 83.8 ± 5.8 years; 52.9% women; MMSE: 14.5 ± 4.2) and 32 age-sex-matched controls with AD without any anti-dementia drug (age: 0.0 ± 6.6 years; MMSE: 23.2 ± 5.3)	Stride time variability decreased (improved) during follow-up in the memantine group (6.3 ± 6.1 versus 3.6 ± 1.3, $p = 0.038$ )

Montero-Odasso et al. (2015) [53]	Before-after design	5 mg/day of donepezil for 1 month, and 5 months with 10 mg/day	5 months	43 patients with mild AD (age: 76.9 ± 8 years; MMSE: 24.63 ± 2; MoCA: 18.5 ± 4)	Gait speed improved from 108.4 ± 18.6 to 113.3 ± 19.5 cm/s ( $p = 0.01$ ); dual-task gait speed from 80.6 ± 23.0 to 85.3 ± 22.3 cm/s ( $p = 0.03$ ). Trail making tests A ( $p = 0.030$ ), B ( $p = 0.001$ ) and B-A ( $p = 0.042$ ) improved after intervention
Montero-Odasso et al. (2019) [54]	RCT, double-blind, placebo-controlled	First month with 5 mg/day of donepezil, and next 5 months with 10 mg/day	6 months	60 patients with MCI (age: 75.3 ± 7 years; MMSE: 27.5 ± 2; MoCA: 23.6 ± 2.5)	Gait speed improved only under dual-task conditions, and there was a reduction in falls, albeit not significant
PD populations					
Auriel et al. (2006) [56]	Open-label, before-after design	Before and 2 h after taking a single dose of 20 mg of MPH	2 h	21 participants with PD who received L-dopa, (age: 70.2 ± 9.2 years; MMSE: 28.8 ± 1.7)	Improvement in attention ( $p = 0.025$ ), EF index showed only a trend ( $p = 0.09$ ). Improvements in Timed Up and Go ( $p = 0.001$ ), gait speed ( $p = 0.005$ ), and stride time variability ( $p = 0.013$ )
Chung et al. (2010) [57]	Randomized, crossover, double-blind	Donepezil vs. placebo. 5 mg/day of donepezil or placebo for 3 weeks, and increase to 10 mg/day for the remaining 3 weeks	6 weeks, 3 weeks washout, 6 weeks of placebo	23 participants with PD who reported falling or nearly falling (age: 68.3 ± 10.8 years; MMSE: 27.6 ± 4.5)	Less falls with donepezil than placebo ( $p = 0.049$ ). Participants with the most falls at baseline tended to show the largest improvements. No differences found in Balance Confidence, Berg Balance, UPDRS III, or MMSE tests
Henderson et al. (2016) [58]	RCT, double-blind, placebo-controlled	Rivastigmine titrated from 3 mg/day (or placebo); incremented every 4 weeks to a maximum of 12 mg/day at week 13 onwards	8 months	130 patients with mild PD (mean age: 71.9 ± 4.8 years; 1.2; MoCA: 25 ± 1.4); half in the intervention groups and half in the placebo group	Intervention improved gait speed (greatest effect) and dual-task gait speed. Stride time variability decreased (improved) not significantly. Falls rate (secondary outcome) was significantly lower in intervention group

Modified and updated from Montero-Odasso and Speechley [55]  
Note: AD Alzheimer’s disease, EF executive function, MCI mild cognitive impairment, MMSE Mini-Mental State Examination, MoCA Montreal Cognitive Assessment, MPH methylphenidate, PD Parkinson’s disease, UPDRS unified Parkinson’s disease, UPDRS unified Parkinson’s disease rating scale

in depth in Chap. 20 in the Part IV of this book. Here we will refer to a few seminal studies that have established that pharmacological improving of cognition may reduce falls.

### **Studies in Cognitively Normal Populations**

A pilot RCT conducted by Ben-Itzhak et al. with 26 community-dwelling older adults showed that methylphenidate, an attentional enhancer drug, improved executive function, gait speed, and gait variability [48]. Another RCT conducted by Shorer et al. showed that a single dose of MPH improved gait and postural stability in 30 healthy older adults and reduced the step errors and step error rate on gait in both single and dual tasks [49]. These findings support the role of drugs aimed at enhancing attention as a therapeutic option for reducing fall risk.

A number of neurotransmitters that have been targeted to improve gait performance, and reduce fall risk, are shared between cognitive function and gait brain motor control. A detailed description of these neurotransmitter pathways is reviewed in Chap. 20. In brief, selective attention, memory, gait motor control and balance are regulated by central cholinergic neurotransmission [50]. Cholinergic brain neurons are found in the hippocampus, nucleus basalis of Meynert, basal ganglia, thalamus, and pedunculopontine nucleus. Thalamic cholinergic activity, which derives mainly from terminals of pedunculopontine nucleus neurons, controls the movement patterns during gait performance. Importantly, central acetylcholine denervation is associated with slow gait and falls in aging, independently of cognitive status, as well as in Parkinson's disease [51]. Thus, improvement of motor function and reduction of fall risk through both cognitive and non-cognitive mechanisms could potentially be achieved by correcting the cholinergic loss seen in aging and neurodegeneration [50].

### **Studies in Cognitively Impaired Populations**

Cholinesterase inhibitors (ChEI), such as donepezil, galantamine, and rivastigmine, are currently used for treatment symptoms in mild to moderate AD and vascular dementia. It has been suggested that ChEIs can improve cortical gait control by enhancing executive function and attention, through an increase of cortical and hippocampal acetylcholine, and improve stride-to-stride variability by a motor enhancement that increases pedunculopontine nucleus neurons' cholinergic activity [50].

The potential effect of galantamine (Assal et al. [52]) and donepezil (Montero-Odasso et al. [50]) to improve gait performance in older adults with mild AD has been shown in two pilot studies. A subsequent open-label trial in 43 older adults with mild AD found that 4 months of treatment with donepezil significantly improved gait speed and dual-task gait speed [53]. Stride time variability showed improvement, although not statistically significant. Participants also experienced significant improvements in executive function, suggesting that the observed gait improvements could be cognitively mediated. A well-designed double-blind, placebo-controlled trial randomized 60 older adults with MCI to receive donepezil or placebo [54]. After 6 months, the donepezil group experienced an improvement in dual-task gait

speed, although this was not statistically significant, and a significant improvement in dual-task gait cost in counting backward by 1 and 7 compared with placebo in the intention-to-treat analysis. Per-protocol analyses showed that all three dual-task costs improved in the donepezil group along with a nonsignificant reduction of rate of falls. These positive results need to be taken with caution since this trial was originally powered for 120 participants, but due to recruitment challenges, only 60 participants were included. However, it is showing a signal that ChEis can improve gait in MCI, particularly dual-task gait performance that relies on the cognitive-motor interface [54]. In an open-label memory clinic study conducted by Beauchet et al. in older participants with AD, memantine, a cognitive enhancer that reduces glutamate neurotransmission, decreased stride time variability [55].

Methylphenidate has also been tested to improve motor function in older adults with cognitive impairments. In a pilot study conducted by Auriel et al. in 21 participants with PD, a single dose of methylphenidate significantly improved attention, executive function, gait velocity, the Timed Up and Go Test, and stride time variability [56]. The effect of ChE inhibitors has also been tested in older adults with PD. Chung et al. conducted a randomized crossover study in 23 older participants with PD where participants taking donepezil had a 50% reduction of fall frequency compared to placebo [57]. A larger well-designed placebo-controlled RCT conducted by Henderson et al. in 130 older participants with PD found that participants randomly assigned to a rivastigmine group improved step time variability during normal and dual-task walking, and reduced their fall rate compared to the placebo group, after 8 months of treatment [58].

In sum, pharmacological cognitive enhancement in MCI and AD has been shown as a promising avenue to improve gait, even though the results in these trials were modest. Conversely, randomized and well-constructed controlled trials showed that cognitive enhancement in older adults with PD led to improvements in gait parameters and decrease in fall rates.

---

## Implications for Practice and Research

Cognitive deficits, as a fall risk factor, should be considered a continuum from normal aging to advanced dementia, and executive function and attention should be evaluated during the routine fall risk assessment. Specific groups, such as older adults with MCI, are at high risk of falls and should be prioritized for fall prevention interventions. Gait assessment under dual tasking can be used to evaluate the impact of cognitive deficits in motor and gait regulations and predict falls, particularly, in older adults with relatively normal gait speed [35]. Therapeutically, improving attention and executive function performance can be a complementary way to treat gait motor control deficits and prevent falls. In the cognitively impaired, this may be critical to reducing their fall risk. It is unclear whether the pharmacologic or the cognitive-exercise training approaches would have a synergistic effect when combined or if one will replace the other; large and controlled trials designed to test this interaction are needed.



**Acknowledgments** The authors would like to thank Dr. Yanina Sarquis-Adamson for her help with editing this chapter. Funding Sources: Dr. Montero-Odasso's program in "Gait and Brain Health" is supported by grants from the Canadian Institute of Health and Research (CIHR), the Ontario Ministry of Research and Innovation, the Ontario Neurodegenerative Diseases Research Initiative (ONDRI), the Canadian Consortium in Neurodegeneration in Aging (CCNA), and the Department of Medicine Program of Experimental Medicine (POEM) Research Award, University of Western Ontario. He is the first recipient of the Schulich Clinician-Scientist Award and holds the CIHR Investigator Award. Dr. Richard Camicioli is funded by CIHR through the Canadian Consortium in Neurodegeneration in Aging (CCNA) as the Lewy Body Team Lead by Brain Canada/CIHR (Functional Assessment of Vascular Reactivity) site lead.

## References

1. Isaacs B. Are falls a manifestation of brain failure? *Age Ageing*. 1978;7(Suppl):97–111.
2. Isaacs B. The giants of geriatrics. In: *The challenge of geriatric medicine*. Oxford: Oxford University Press; 1992. p. 1–7.
3. Montero-Odasso M, Bherer L, Studenski S, et al. Mobility and cognition in seniors. Report from the 2008 Institute of Aging (CIHR) mobility and cognition workshop. *Can Geriatr J*. 2015;18(3):159–67.
4. Isaacs B, Caird FI. "Brain failure": a contribution to the terminology of mental abnormality in old age. *Age Ageing*. 1976;5(4):241–4.
5. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60(11):2127–36.
6. van Iersel MB, Hoefsloot W, Munneke M, Bloem BR, Olde Rikkert MG. Systematic review of quantitative clinical gait analysis in patients with dementia. *Z Gerontol Geriatr*. 2004;37(1):27–32.
7. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319(26):1701–7.
8. Morris JC, Rubin EH, Morris EJ, Mandel SA. Senile dementia of the Alzheimer's type: an important risk factor for serious falls. *J Gerontol*. 1987;42(4):412–7.
9. Hajek A, Konig HH. The association of falls with loneliness and social exclusion: evidence from the DEAS German Ageing Survey. *BMC Geriatr*. 2017;17(1):204.
10. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture*. 2002;16(1):1–14.
11. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329–42.
12. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci*. 2010;65(10):1086–92.
13. Hausdorff JM, Yogev G, Springer S, Simon ES, Giladi N. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res*. 2005;164(4):541–8.
14. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299–308.
15. Liu-Ambrose TY, Ashe MC, Graf P, Beattie BL, Khan KM. Increased risk of falling in older community-dwelling women with mild cognitive impairment. *Phys Ther*. 2008;88(12):1482–91.
16. Verghese J, Robbins M, Holtzer R, et al. Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc*. 2008;56(7):1244–51.
17. Montero-Odasso M, Bergman H, Phillips NA, Wong CH, Sourial N, Chertkow H. Dual-tasking and gait in people with mild cognitive impairment. The effect of working memory. *BMC Geriatr*. 2009;9:41.

18. Delbaere K, Kochan NA, Close JC, et al. Mild cognitive impairment as a predictor of falls in community-dwelling older people. *Am J Geriatr Psychiatry*. 2012;20(10):845–53.
19. Muir SW, Speechley M, Wells J, Borrie M, Gopaul K, Montero-Odasso M. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges across the cognitive spectrum. *Gait Posture*. 2011;35(1):96–100.
20. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil*. 2001;82(8):1050–6.
21. Oh ES, Blennow K, Bigelow GE, et al. Abnormal CSF amyloid-beta42 and tau levels in hip fracture patients without dementia. *PLoS One*. 2018;13(9):e0204695.
22. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci*. 2014;69(11):1375–88.
23. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: implications for risk assessment and prevention. *J Am Geriatr Soc*. 2018;66(2):367–75.
24. Maki BE, McIlroy WE. Postural control in the older adult. *Clin Geriatr Med*. 1996;12(4):635–58.
25. Fasano A, Plotnik M, Bove F, Berardelli A. The neurobiology of falls. *Neurol Sci*. 2012;33(6):1215–23.
26. Holtzer R, Wang C, Verghese J. Performance variance on walking while talking tasks: theory, findings, and clinical implications. *Age (Dordr)*. 2014;36(1):373–81.
27. Bloem BR, Grimbergen YA, van Dijk JG, Munneke M. The “posture second” strategy: a review of wrong priorities in Parkinson's disease. *J Neurol Sci*. 2006;248(1–2):196–204.
28. Holtzer R, Verghese J, Allali G, Izzetoglu M, Wang C, Mahoney JR. Neurological gait abnormalities moderate the functional brain signature of the posture first hypothesis. *Brain Topogr*. 2016;29(2):334–43.
29. van Iersel MB, Verbeek AL, Bloem BR, Munneke M, Esselink RA, Rikkert MG. Frail elderly patients with dementia go too fast. *J Neurol Neurosurg Psychiatry*. 2006;77(7):874–6.
30. Kim SL, Lee MJ, Lee MS. Cognitive dysfunction associated with falls in progressive supranuclear palsy. *Gait Posture*. 2014;40(4):605–9.
31. Lundin-Olsson L, Nyberg L, Gustafson Y. “Stops walking when talking” as a predictor of falls in elderly people. *Lancet*. 1997;349(9052):617.
32. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil*. 2012;93(2):293–9.
33. Hicks RE, Bradshaw GJ, Kinsbourne M. Vocal-manual trade-offs in hemispheric sharing of human performance control. *J Mot Behav*. 1978;10(1):1–6.
34. Verghese J, Wang C, Ayers E, Izzetoglu M, Holtzer R. Brain activation in high-functioning older adults and falls: prospective cohort study. *Neurology*. 2017;88(2):191–7.
35. Muir-Hunter SW, Wittwer JE. Dual-task testing to predict falls in community-dwelling older adults: a systematic review. *Physiotherapy*. 2016;102(1):29–40.
36. Oliver D, Connelly JB, Victor CR, et al. Strategies to prevent falls and fractures in hospitals and care homes and effect of cognitive impairment: systematic review and meta-analyses. *BMJ*. 2007;334(7584):82.
37. Hauer K, Becker C, Lindemann U, Beyer N. Effectiveness of physical training on motor performance and fall prevention in cognitively impaired older persons: a systematic review. *Am J Phys Med Rehabil*. 2006;85(10):847–57.
38. Verghese J, Mahoney J, Ambrose AF, Wang C, Holtzer R. Effect of cognitive remediation on gait in sedentary seniors. *J Gerontol A Biol Sci Med Sci*. 2010;65(12):1338–43.
39. Smith-Ray RL, Hughes SL, Prohaska TR, Little DM, Jurivich DA, Hedeker D. Impact of cognitive training on balance and gait in older adults. *J Gerontol B Psychol Sci Soc Sci*. 2015;70(3):357–66.
40. Silsupadol P, Shumway-Cook A, Lugade V, et al. Effects of single-task versus dual-task training on balance performance in older adults: a double-blind, randomized controlled trial. *Arch Phys Med Rehabil*. 2009;90(3):381–7.
41. Falbo S, Condello G, Capranica L, Forte R, Pesce C. Effects of physical-cognitive dual task training on executive function and gait performance in older adults: a randomized controlled trial. *Biomed Res Int*. 2016;2016:5812092.

42. van het Reve E, de Bruin ED. Strength-balance supplemented with computerized cognitive training to improve dual task gait and divided attention in older adults: a multicenter randomized-controlled trial. *BMC Geriatr*. 2014;14:134.
43. You JH, Shetty A, Jones T, Shields K, Belay Y, Brown D. Effects of dual-task cognitive-gait intervention on memory and gait dynamics in older adults with a history of falls: a preliminary investigation. *NeuroRehabilitation*. 2009;24(2):193–8.
44. Schwenk M, Zieschang T, Oster P, Hauer K. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology*. 2010;74(24):1961–8.
45. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *J Gerontol A Biol Sci Med Sci*. 2011;66(2):234–40.
46. Mirelman A, Rochester L, Maidan I, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet*. 2016;388(10050):1170–82.
47. van Ooijen MW, Roerdink M, Trekop M, Janssen TW, Beek PJ. The efficacy of treadmill training with and without projected visual context for improving walking ability and reducing fall incidence and fear of falling in older adults with fall-related hip fracture: a randomized controlled trial. *BMC Geriatr*. 2016;16(1):215.
48. Ben Itzhak R, Giladi N, Gruendlinger L, Hausdorff JM. Can methylphenidate reduce fall risk in community-living older adults? A double-blind, single-dose cross-over study. *J Am Geriatr Soc*. 2008;56(4):695–700.
49. Shorer Z, Bachner Y, Guy T, Melzer I. Effect of single dose methylphenidate on walking and postural stability under single- and dual-task conditions in older adults--a double-blind randomized control trial. *J Gerontol A Biol Sci Med Sci*. 2013;68(10):1271–80.
50. Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. *J Am Geriatr Soc*. 2009;57(2):359–60.
51. Pelosin E, Ogliastro C, Lagravinese G, et al. Attentional control of gait and falls: is cholinergic dysfunction a common substrate in the elderly and Parkinson's disease? *Front Aging Neurosci*. 2016;8:104.
52. Assal F, Allali G, Kressig RW, Herrmann FR, Beauchet O. Galantamine improves gait performance in patients with Alzheimer's disease. *J Am Geriatr Soc*. 2008;56(5):946–7.
53. Montero-Odasso M, Muir-Hunter SW, Oteng-Amoako A, et al. Donepezil improves gait performance in older adults with mild Alzheimer's disease: a phase II clinical trial. *J Alzheimers Dis*. 2015;43(1):193–9.
54. Montero-Odasso M, Speechley M, Chertkow H, et al. Donepezil for gait and falls in mild cognitive impairment: a randomized controlled trial. *Eur J Neurol*. 2019;26(4):651–9.
55. Beauchet O, Launay C, Fantino B, Annweiler C, Allali G. Does memantine improve the gait of individuals with Alzheimer's disease? *J Am Geriatr Soc*. 2011;59(11):2181–2.
56. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin Neuropharmacol*. 2006;29(1):15–7.
57. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. *Neurology*. 2010;75(14):1263–9.
58. Henderson EJ, Lord SR, Brodie MA, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016;15(3):249–58.
59. Yogev-Seligmann G, Giladi N, Brozgov M, Hausdorff JM. A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil*. 2012;93(1):176–81.

# Dismobility in Aging and the Role of Cognition and Health Consequences of Reduced Mobility

## 2

Qu Tian and Stephanie A. Studenski

---

### Introduction

Cognition plays a key role in reduced mobility, a major risk factor for falls [1]. In addition, mobility decline predicts cognitive impairment, which also increases fall risk. Thus, fall prevention requires a thorough understanding of the interplay among mobility, cognition, and aging. Although “dismobility” strongly predicts multiple adverse health outcomes, including falls, it is not yet widely recognized by clinicians and is often neglected in medical practice. In order to better evaluate and treat fall risk, the clinician requires knowledge and skills relevant to dismobility and how it relates to cognitive function in aging.

This chapter will focus on two major topics: (1) dismobility in aging, including terminology, assessment, and clinical consequences, and (2) the role of the aging brain in cognition and movement.

Specifically, we begin with a description of dismobility in aging and then discuss health consequences and role in other geriatric syndromes, such as sarcopenia and frailty. We then summarize empirical evidence about aging brain structure and function at the interface of movement and cognition.

---

Q. Tian

Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging,  
Baltimore, MD, USA

e-mail: [qu.tian@nih.gov](mailto:qu.tian@nih.gov)

S. A. Studenski (✉)

Longitudinal Studies Section, Translational Gerontology Branch, National Institute on Aging,  
Baltimore, MD, USA

University of Pittsburgh, Pittsburgh, PA, USA

e-mail: [stephanie.studenski@nih.gov](mailto:stephanie.studenski@nih.gov)

## What Is Dismobility?

### The Definition

Dismobility is a proposed diagnostic term for impaired mobility, defined as a gait speed of 0.6 m/s or slower [2]. A gait speed of 0.6 m/s or slower is increasingly common in advanced old age and increases the probability of adverse health outcomes dramatically. Since gait speed is a powerful predictor of mobility and cognitive problems and is relatively simple to measure in clinical settings, clinicians should consider routinely assessing for and diagnosing dismobility. Dismobility is not identical with mobility limitations or mobility disability, which is often defined based on a self-report of difficulty or inability to perform common mobility tasks such as walking short or long distances or climbing stairs. Inconsistencies among terms can lead to difficulty interpreting findings across studies.

### How to Measure Mobility?

In both research and clinical settings, mobility can be measured using self-report questionnaires and performance-based tasks [3, 4]. Mobility is a general umbrella term, including subdomains, such as gait, lower extremity physical performance, and balance. Table 2.1 presents measurement examples in each domain.

### Interpreting Gait Speed

While gait speed has been assessed using multiple distances as well as at usual or fast speeds, and standing start or constant velocity, the most common and clinically feasible approach is the 4-m usual gait speed from a standing start, using timing from the word “go” to when a foot crosses the 4-m line. Using this approach, a speed of 1.0 m/s or faster is generally considered “good,” while a speed of 0.6 m/s or slower is clearly “slow.” Using these cutpoints, the 4-m time should be 4 s or less to be equivalent to 1.0 m/s, and a time of more than 6 s indicates slow walking. Cross-sectionally, speeds of 1.0 m/s are rarely found in persons with ADL disability, whereas those with gait speeds of 0.6 m/s or slower are rarely independent in ADL and IADL. Therefore, clinicians could consider a comprehensive geriatric assessment in all older adults with gait speeds of 0.6 m/s or slower in order to look for remediable deficits and to assess need for social support.

### Multisystem Causes of Dismobility

Dismobility is often a consequence of impairments in multiple organ systems, including cardiopulmonary, musculoskeletal, and central and peripheral nervous systems as well as others such as anemia, depression, obesity, and pain.

**Table 2.1** Examples of mobility measures

	Self-report		Performance-based	
	Measures	Description	Measures	Description
Gait			Walking speed	Various distances from 3 to 50 m at usual or rapid pace
			Endurance walk time	400-m walk, 6-min walk, tandem walking speed
Lower extremity physical function	“How much difficulty do you have walking 1/4, 1/2, 1 mile? Climbing steps?” Rosow-Breslau [5] and Nagi scales [6] NIH toolbox for self-report and performance Activities of daily living (ADL) by the Barthel Index [7]; instrumental ADL by Lawton’s scale [8]	Ability to do heavy household work; ability to walk 1/4 or 1/2 mile	Short physical performance battery [9] Health ABC physical performance battery	Standing balance, walking speed, and ability to rise from a chair
Balance	Activities-specific balance confidence (ABC) scale	Self-rated confidence levels of various activities	Timed Up and Go [10]	Time to rise from an arm chair, walk 3 m, turn, walk back, and sit back down
			Berg balance test [11, 12]	14-item balance activities
			Standing balance time	
			Postural sway	

For instance, an impaired central nervous system, reflected by cognitive decline, with brain atrophy and white matter change, is associated with poorer mobility and mobility decline [13–15]. Poorer cardiopulmonary function, lower muscle strength, and poorer balance are associated with reduced mobility and the development of mobility disability [16, 17]. Poorer sensorimotor function, higher anticholinergic burden, and lower insulin resistance are associated with slower gait [18–20]. Overall, the extent of comorbidity is associated with mobility decline and mobility disability [21–23].

**How Does Dismobility Differ from Mobility Disability, Sarcopenia, or Frailty?**

Dismobility, as defined by Cummings et al., uses a single gait speed cut point of 0.6 m/s or slower. It is not necessarily the same as mobility disability, which is defined as a self- or other report of difficulty or inability to move the body as a

**Table 2.2** Examples of geriatric syndromes of sarcopenia and frailty that include gait speed

Year	Terminology	Reference
1997	Sarcopenia: describes important changes in body composition and related functions	Rosenberg [24]
2004–2005	Frailty: being weak, poor endurance, weight loss, low physical activity, slow gait speed	Fried et al. [25]
2005	Frailty: cumulative index of conditions, function and physiologic indicators; elements vary among indices	Rockwood et al. [26]
2010	Sarcopenia: EWGSOP: low muscle mass; low muscle strength or low performance	Cruz-Jentoft et al. [27]
2011	Sarcopenia: IWGS: low muscle mass; low gait speed of <1.0 m/s	Fielding et al. [28]
2010	Sarcopenia: ESPEN SIG: low muscle mass; low gait speed of <0.8 m/s	Muscaritoli et al. [29]
2014	Sarcopenia: FNIH: low muscle mass; low muscle strength	Studenski et al. [30]

Note: *EWGSOP* European Working Group on Sarcopenia in Older People, *IWGS* International Working Group on Sarcopenia, *ESPEN SIG* European Society for Clinical Nutrition and Metabolism Special Interest Groups, *FNIH* Foundation for the National Institutes of Health

whole. Thus, a person could have dismobility or mobility disability together or separately. Slow gait speed is also sometimes used as a component in the definition of geriatric syndromes, including frailty, and is associated with sarcopenia. Table 2.2 lists examples of definitions of geriatric syndromes that include gait speed as a component.

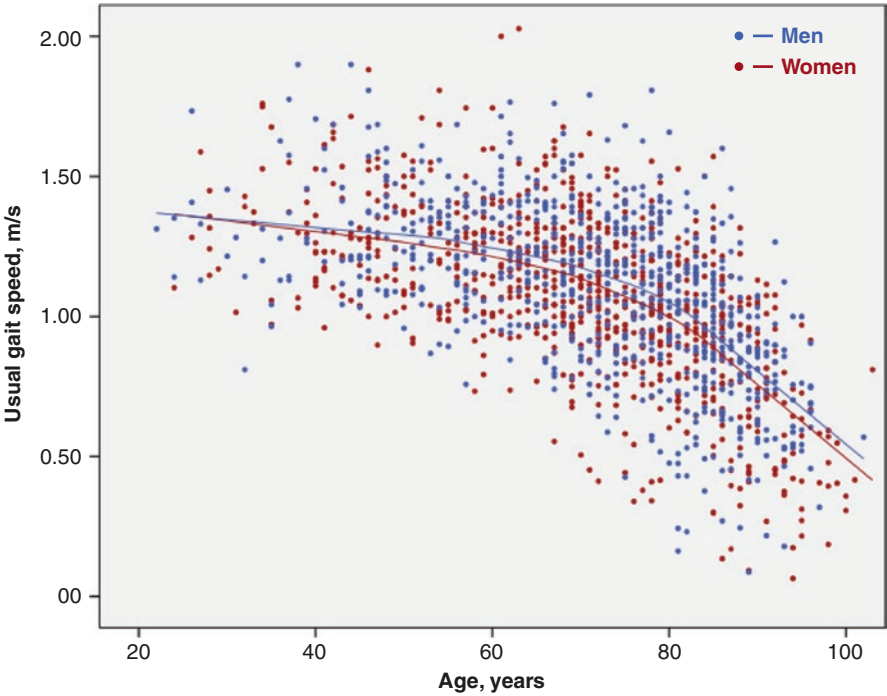
### The Age Effect on Dismobility

Gait speed declines with age and the rate of decline generally accelerates after age 70 [31, 32]. Figure 2.1 shows gait speed as a function of age by sex in the Baltimore Longitudinal Study of Aging. The prevalence of dismobility, defined as gait speed 0.6 m/s or slower, also increases with advancing age, accelerating after age 70 [2]. Figure 2.2 shows the prevalence of dismobility by age and sex using data reported from Cummings et al. [2]. Gait patterns also change with age [33]. Age-related declines in mobility and postural control increase fall risk [1]. A history of falls, in turn, reduces the ability to effectively recover from a sudden perturbation.

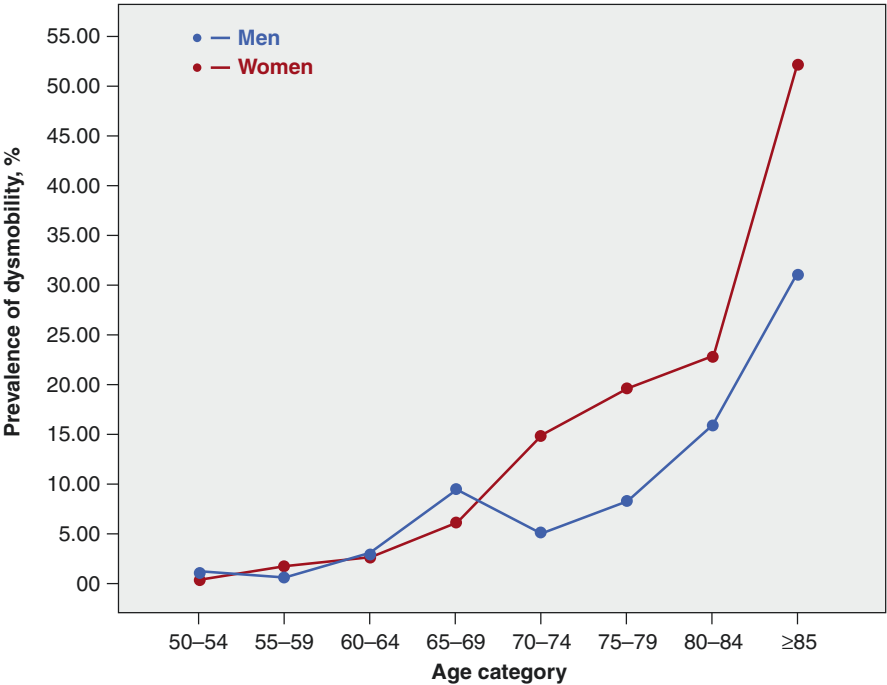
## Health Consequences of Reduced Mobility

### Clinical Consequences

Reduced mobility performance can precede mobility disability and it also helps predict dementia. Both mobility and cognitive impairment contribute to loss of independence in late life. Clinicians need a solid understanding of the clinical consequences of reduced mobility.



**Fig. 2.1** Usual gait speed as a function of age by sex



**Fig. 2.2** Prevalence of dismobility by age category and sex



Various mobility performance measures, such as gait speed, lower extremity motor function, and long-distance corridor walking performance, predict mobility limitation, subsequent mobility disability, and incident disability across various older cohorts [34–37]. Gait speed also predicts declines in motor ability among mild-to-moderately disabled older persons who had some difficulty in upper and lower extremity functions [38].

While mobility status plays no role yet in the diagnosis of cognitive impairment or dementia, poor mobility has repeatedly been associated with cognitive decline [39–41] and risk for cognitive impairment and dementia [42–44], suggesting an emerging role to aid in diagnoses.

Reduced mobility is a consistent and powerful predictor of fall risk [45, 46]. The combination of mobility problems with cognitive problems increases fall risk further [47].

### **Survival, Health-Care Use, Cognitive Impairment, Dementia, and Functional Status**

Poor self-reported mobility and reduced physical performance predict hospitalization [34, 48], length of stay in hospital [49], rehospitalization [50], and nursing home admission [9].

Reduced mobility, including gait speed and other physical performance measures, predicts disability and mortality in older adults. With every 0.1 m/s slower gait speed, 3-year disability increases by about 30% and mortality increases by 12% [36, 51]. Reduced mobility also predicts cognitive impairment and dementia [42, 43], which increases fall risk [52]. Reduced mobility probably also limits the ability to access health care services that require traveling or walking substantial distances, which could potentially delay treatment.

### **Physiological and Psychological Consequences**

Various disablement models including Nagi, NHATS, and ICF models have been used to provide a conceptual framework for the evaluation and management of mobility problems [53]. In all of them, mobility is a whole-body activity that is influenced by many diseases and system impairments, modified by factors outside the individual and a major contributor to limitations in social and role functions. In the Nagi model, which is often used in geriatrics [54], reduced mobility would fall into the “functional limitations” phase. Physiological and psychological factors are both causes and consequences of reduced mobility, and other factors such as the environment and social support may modify mobility disability. For instance, poor physical function, including reduced mobility, predicts depressive symptoms in older adults [55–58]. Slow gait speed also predicts fear of falling [59] and predicts fall, which may lead to hip fractures [60]. Cardiopulmonary

endurance, musculoskeletal problems, and nervous system disorders commonly contribute to mobility problems. Other factors include sensory disorders, mood disorders, sleep problems, and anemia [61].

## **Social Consequences**

While evidence is limited, lower mobility is associated with lower social engagement of activities outside the home and in-home among older adults without disability [62]. This study also shows disability is associated with lower social engagement, and this relationship differs by types of activity. Future research is warranted to understand longitudinal changes in social engagement following reduced mobility.

## **Public Health Action Proposals to Prevent Dismobility**

Two main types of mobility are often recognized among community-dwelling older adults, walking and driving [63]. Both individual capacity and environmental factors contribute to reduced mobility [64]. Current public health interventions to prevent dismobility or to promote mobility are limited in targeting one form of mobility and primarily focusing on modifications of individual capacity.

Although environmental factors are less easy to modify than individual capacity, recent data show the improved amount of walking when older adults are provided with safe walking routes and counseling to self-manage physical activity [65]. This ecological approach suggests that a multilevel intervention targeting individual, social, and environmental factors will lead to the most effective outcomes, such as changes in physical activity [66].

Based on the ecological model, public health action proposals to prevent dismobility are to connect and collaborate with other disciplines and fields, such as urban design, city planning, and transportation science [67].

---

## **The Role of the Aging Brain in Cognition and Mobility**

### **Brain Structure and Function at the Interface of Cognition and Movement: The Cognitive Mechanism Underlying Reduced Mobility**

Both aging itself and common forms of neuropathology contribute to decline in cognition and mobility and increase the risk of future clinically significant cognitive impairment and dismobility. Cognition itself plays a key role in reduced mobility because being mobile requires the integrity of cognitive functions for multiple aspects such as planning, navigating, and obstacle avoidance. Accumulating evidence suggests that

cognition, measured either by global cognition or specific cognitive domains, is strongly associated with current and future mobility in older adults.

Domains that show relationships with mobility include attention, executive function, memory, visuospatial ability, and processing speed [13, 68]. Studies to date often lack a thorough evaluation of multiple aspects of cognition; they either only evaluate global cognition or a single cognitive domain. The specific relationships between aspects of mobility and individual cognitive domains are not yet well understood. Existing evidence suggests that fluid cognition, such as attention and executive function, but not crystallized intelligence, such as language, strongly affects mobility. One recent meta-analysis of multiple individual studies found an overall association between cognition and mobility that was relatively small but statistically significant [68]. This diversity of findings may be due to factors such as study design and duration, study sample, or the specific cognitive and mobility measures applied. In the meta-analysis, among cognitive domains examined, executive function showed the strongest association with mobility. Among mobility measures (e.g., gait speed, lower extremity function, balance), balance has rarely been associated with cognition.

While in usual aging the relationship between cognitive and motor function is well established based on cross-sectional studies, longitudinal studies remain limited. Thus, the temporal sequence of development of problems with the aging brain, cognition, and mobility is not well understood. The small number of existing longitudinal studies that focus on prediction and the temporal sequence between mobility and cognition have had mixed findings. These discrepancies are likely due to (but not limited to) different sample characteristics, the sample's initial mobility and cognitive status, different measures of cognition and mobility, and various follow-up times. Due to aging and shared neuropathology, declines in cognition and mobility may co-occur. To understand the temporal sequence between cognition and mobility, it is essential to examine an "incidence cohort" with initially unimpaired cognition and mobility. A recent study attempts to address the temporal sequence between cognition and mobility in a well-characterized "incidence cohort" with initially unimpaired cognition and mobility [41]. This longitudinal study shows that there was a bidirectional relationship between usual gait speed and executive function. However, there was only a one-way relationship between performance on a challenging mobility task, such as the 400-m walk and subsequent cognitive decline. Specifically, 400-m walk performance predicted subsequent executive function and verbal memory, but cognition did not predict subsequent 400-m walk performance. These findings suggest that challenging mobility performance may be an early predictor of subsequent cognitive decline during typical aging.

The role of the aging brain in reduced mobility, balance control, and falls is evident in neuroimaging studies (for reviews, see [69, 70]). The relationship with reduced mobility is observed in both gray matter and white matter, especially areas important for sensorimotor integration. In older adults, neural substrates underlying poorer mobility performance include macroscopic measures of brain volumes, the microstructural integrity of gray matter and white matter, white matter hyperintensities, and  $\beta$ -amyloid burden [71–73]. Studies also reported a threshold effect of white

matter hyperintensities on gait disturbance, reduced mobility and balance [74–77], and mobility decline [78–81].

Several studies attempted to examine whether cognitive function mediates the relationship between neural substrates and mobility [82–84]. Although cross-sectional, findings suggest that executive function may mediate the prediction of gray and white matter health to mobility performance. Future longitudinal studies are warranted to examine this mediation pathway.

## The Role of Cognitive Reserve in Reduced Mobility

Conceptually, cognitive reserve (CR) is defined as a process to cope with brain pathology by either using existing cognitive resources efficiently or by utilizing alternative cognitive processes. Measures of CR in general capture lifetime experience, such as educational level, socioeconomic status, degree of literacy, and verbal intelligence quotient (IQ).

These proxies of CR are reported to be associated with mobility performance. For instance, higher verbal IQ is associated with faster gait speed [85, 86]. Another study showed CR, measured as performance on a vocabulary test, moderated the association between visuoperceptual speed and mobility [87]. The relationship between visuoperceptual speed and mobility decline is greater in older adults with higher CR than those with lower CR. Socioeconomic status, such as childhood socioeconomic position, manual occupation, and less skilled occupation, is also associated with poorer gait speed and physical function, even accounting for health-related factors [88–91]. Higher education level is associated with faster gait speed in both men and women [92, 93].

## What Important Questions Remain Unanswered?

In recent years, this field has been rapidly growing. However, mechanistic and longitudinal studies are still sparse. Animal models of aging and mobility are an area of growing interest. The role of body composition, especially lean mass and fat mass, continues to have complex and unclear relationships with strength and mobility. The independent role of aspects of gait, such as stride length, cadence, and gait variability in mobility, cognition, and falls, is under study and further work remains to be done.

---

## References

1. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. *Maturitas*. 2013;75(1):51–61.
2. Cummings SR, Studenski S, Ferrucci L. A diagnosis of dismobility--giving mobility clinical visibility: a Mobility Working Group recommendation. *JAMA*. 2014;311(20):2061–2.
3. Guralnik JM, et al. Physical performance measures in aging research. *J Gerontol*. 1989;44(5):M141–6.

4. Studenski S, et al. Physical performance measures in the clinical setting. *J Am Geriatr Soc*. 2003;51(3):314–22.
5. Rosow I, Breslau N. A Guttman health scale for the aged. *J Gerontol*. 1966;21(4):556–9.
6. Nagi SZ. An epidemiology of disability among adults in the United States. *Milbank Mem Fund Q Health Soc*. 1976;54(4):439–67.
7. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J*. 1965;14:61–5.
8. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9(3):179–86.
9. Guralnik JM, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85–94.
10. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the “get-up and go” test. *Arch Phys Med Rehabil*. 1986;67(6):387–9.
11. Berg K, Wood-Dauphinee S, Williams JI. The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. *Scand J Rehabil Med*. 1995;27(1):27–36.
12. Berg KO, et al. Measuring balance in the elderly: validation of an instrument. *Can J Public Health*. 1992;83 Suppl 2:S7–11.
13. Morris R, et al. Gait and cognition: mapping the global and discrete relationships in ageing and neurodegenerative disease. *Neurosci Biobehav Rev*. 2016;64:326–45.
14. Callisaya ML, et al. Brain structural change and gait decline: a longitudinal population-based study. *J Am Geriatr Soc*. 2013;61(7):1074–9.
15. Callisaya ML, et al. Longitudinal relationships between cognitive decline and gait slowing: the Tasmanian Study of Cognition and Gait. *J Gerontol A Biol Sci Med Sci*. 2015;70(10):1226–32.
16. Buchman AS, et al. Pulmonary function, muscle strength, and incident mobility disability in elders. *Proc Am Thorac Soc*. 2009;6(7):581–7.
17. Cuoco A, et al. Impact of muscle power and force on gait speed in disabled older men and women. *J Gerontol A Biol Sci Med Sci*. 2004;59(11):1200–6.
18. Callisaya ML, et al. A population-based study of sensorimotor factors affecting gait in older people. *Age Ageing*. 2009;38(3):290–5.
19. Kuo CK, et al. Inverse association between insulin resistance and gait speed in nondiabetic older men: results from the U.S. National Health and Nutrition Examination Survey (NHANES) 1999–2002. *BMC Geriatr*. 2009;9(9):49.
20. Nebes RD, et al. Serum anticholinergic activity and motor performance in elderly persons. *J Gerontol A Biol Sci Med Sci*. 2007;62(1):83–5.
21. Cesari M, et al. Comorbidity and physical function: results from the aging and longevity study in the Sirente geographic area (iSIRENTE study). *Gerontology*. 2006;52(1):24–32.
22. Fried LP, et al. Association of comorbidity with disability in older women: the Women’s Health and Aging Study. *J Clin Epidemiol*. 1999;52(1):27–37.
23. Kriegsman DM, Deeg DJ, Stalman WA. Comorbidity of somatic chronic diseases and decline in physical functioning: the Longitudinal Aging Study Amsterdam. *J Clin Epidemiol*. 2004;57(1):55–65.
24. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr*. 1997;127(5 Suppl):990S–1S.
25. Fried LP, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004;59(3):255–63.
26. Rockwood K, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489–95.
27. Cruz-Jentoft AJ, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39(4):412–23.
28. Fielding RA, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International Working Group on Sarcopenia. *J Am Med Dir Assoc*. 2011;12(4):249–56.

29. Muscaritoli M, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr.* 2010;29(2):154–9.
30. Studenski SA, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci.* 2014;69(5):547–58.
31. Ferrucci L, et al. Age-related change in mobility: perspectives from life course epidemiology and geroscience. *J Gerontol A Biol Sci Med Sci.* 2016;71(9):1184–94.
32. Newman AB, et al. Health and function of participants in the Long Life Family Study: a comparison with other cohorts. *Aging (Albany NY).* 2011;3(1):63–76.
33. Ko S, et al. Age-related mechanical work expenditure during normal walking: the Baltimore Longitudinal Study of Aging. *J Biomech.* 2009;42(12):1834–9.
34. Guralnik JM, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci.* 2000;55(4):M221–31.
35. Newman AB, et al. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA.* 2006;295(17):2018–26.
36. Perera S, et al. Gait speed predicts incident disability: a pooled analysis. *J Gerontol A Biol Sci Med Sci.* 2016;71(1):63–71.
37. Hong S, et al. Slower gait speed predicts decline in Instrumental Activities of Daily Living in community-dwelling elderly: 3-year prospective finding from Living Profiles of Older People Survey in Korea. *J Clin Gerontol Geriatr.* 2016;7(4):141–5.
38. Albert SM, Bear-Lehman J, Anderson SJ. Declines in mobility and changes in performance in the instrumental activities of daily living among mildly disabled community-dwelling older adults. *J Gerontol A Biol Sci Med Sci.* 2015;70(1):71–7.
39. Atkinson HH, et al. Predictors of combined cognitive and physical decline. *J Am Geriatr Soc.* 2005;53(7):1197–202.
40. Onder G, et al. Measures of physical performance and risk for progressive and catastrophic disability: results from the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci.* 2005;60(1):74–9.
41. Tian Q, et al. The relative temporal sequence of decline in mobility and cognition among initially unimpaired older adults: results from the Baltimore Longitudinal Study of Aging. *Age Ageing.* 2017;46(3):445–51.
42. Beauchet O, et al. Poor gait performance and prediction of dementia: results from a meta-analysis. *J Am Med Dir Assoc.* 2016;17(6):482–90.
43. Buracchio T, et al. The trajectory of gait speed preceding mild cognitive impairment. *Arch Neurol.* 2010;67(8):980–6.
44. Camicioli R, et al. Motor slowing precedes cognitive impairment in the oldest old. *Neurology.* 1998;50(5):1496–8.
45. Beauchet O, et al. Timed Up and Go test and risk of falls in older adults: a systematic review. *J Nutr Health Aging.* 2011;15(10):933–8.
46. Dargent-Molina P, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet.* 1996;348(9021):145–9.
47. Montero-Odasso M, et al. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc.* 2012;60(11):2127–36.
48. Inzitari M, et al. Gait speed predicts decline in attention and psychomotor speed in older adults: the health aging and body composition study. *Neuroepidemiology.* 2007;29(3–4):156–62.
49. Volpato S, et al. Performance-based functional assessment in older hospitalized patients: feasibility and clinical correlates. *J Gerontol A Biol Sci Med Sci.* 2008;63(12):1393–8.
50. Volpato S, et al. Predictive value of the Short Physical Performance Battery following hospitalization in older patients. *J Gerontol A Biol Sci Med Sci.* 2011;66(1):89–96.
51. Studenski S, et al. Gait speed and survival in older adults. *JAMA.* 2011;305(1):50–8.
52. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing.* 2012;41(3):299–308.

53. Freedman VA. Adopting the ICF language for studying late-life disability: a field of dreams? *J Gerontol A Biol Sci Med Sci*. 2009;64(11):1172–4; discussion 1175–6.
54. Nagi SZ. Disability concepts revisited; implications for prevention. In: *Disability in America: toward a national agenda for prevention*. Washington, DC: Division of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press; 1991. p. 309–27.
55. Beekman AT, et al. Depression and physical health in later life: results from the Longitudinal Aging Study Amsterdam (LASA). *J Affect Disord*. 1997;46(3):219–31.
56. Forsell Y, et al. Prevalence and correlates of depression in a population of nonagenarians. *Br J Psychiatry*. 1995;167(1):61–4.
57. Kivela SL. Depression and physical and social functioning in old age. *Acta Psychiatr Scand Suppl*. 1994;377:73–6.
58. Lampinen P, Heikkinen E. Reduced mobility and physical activity as predictors of depressive symptoms among community-dwelling older adults: an eight-year follow-up study. *Aging Clin Exp Res*. 2003;15(3):205–11.
59. Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. *J Am Geriatr Soc*. 1997;45(3):313–20.
60. Hayes WC, et al. Etiology and prevention of age-related hip fractures. *Bone*. 1996;18(1 Suppl):77S–86S.
61. Brach J, Rosano C, Studenski S. Mobility. In: Halter J, et al., editors. *Hazzard's geriatric medicine and gerontology*. New York: McGraw-Hill; 2009.
62. Rosso AL, et al. Mobility, disability, and social engagement in older adults. *J Aging Health*. 2013;25(4):617–37.
63. Collla DV, Sharp J, Giesbrecht L. The 2001 National Household Travel Survey: a look into the travel patterns of older Americans. *J Saf Res*. 2003;34(4):461–70.
64. Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med*. 1994;38(1):1–14.
65. Rosenberg D, et al. Feasibility and outcomes of a multilevel place-based walking intervention for seniors: a pilot study. *Health Place*. 2009;15(1):173–9.
66. Satariano WA, McAuley E. Promoting physical activity among older adults: from ecology to the individual. *Am J Prev Med*. 2003;25(3 Suppl 2):184–92.
67. Satariano WA, et al. Mobility and aging: new directions for public health action. *Am J Public Health*. 2012;102(8):1508–15.
68. Demnitz N, et al. A systematic review and meta-analysis of cross-sectional studies examining the relationship between mobility and cognition in healthy older adults. *Gait Posture*. 2016;50:164–74.
69. Holtzer R, et al. Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci*. 2014;69(11):1375–88.
70. Zheng JJ, et al. Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. *Stroke*. 2011;42(7):2086–90.
71. Nadkarni NK, et al. Association of brain amyloid-beta with slow gait in elderly individuals without dementia: influence of cognition and apolipoprotein E epsilon4 genotype. *JAMA Neurol*. 2017;74(1):82–90.
72. Tian Q, et al.  $\beta$ -Amyloid burden predicts lower extremity performance decline in cognitively unimpaired older adults. *J Gerontol A Biol Sci Med Sci*. 2017;72(5):716–23.
73. Wennberg AMV, et al. Longitudinal association between brain amyloid beta and gait in the Mayo Clinic Study of Aging. *J Gerontol A Biol Sci Med Sci*. 2018;73(9):1244–50.
74. Baezner H, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. *Neurology*. 2008;70(12):935–42.
75. Guttmann CR, et al. White matter abnormalities in mobility-impaired older persons. *Neurology*. 2000;54(6):1277–83.
76. Srikanth V, et al. Cerebral white matter lesions, gait, and the risk of incident falls: a prospective population-based study. *Stroke*. 2009;40(1):175–80.
77. Blahak C, et al. Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: cross sectional results from the LADIS study. *J Neurol Neurosurg Psychiatry*. 2009;80(6):608–13.



78. Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch Neurol*. 2003;60(6):835–9.
79. Kerber KA, et al. Disequilibrium in older people: a prospective study. *Neurology*. 1998;51(2):574–80.
80. Rosano C, et al. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc*. 2005;53(4):649–54.
81. Whitman GT, et al. A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. *Neurology*. 2001;57(6):990–4.
82. Bollandzadeh N, et al. Pathways linking regional hyperintensities in the brain and slower gait. *NeuroImage*. 2014;99:7–13.
83. Nadkarni NK, et al. Association between cerebellar gray matter volumes, gait speed, and information-processing ability in older adults enrolled in the Health ABC study. *J Gerontol A Biol Sci Med Sci*. 2014;69(8):996–1003.
84. Rosano C, et al. Slower gait, slower information processing and smaller prefrontal area in older adults. *Age Ageing*. 2012;41(1):58–64.
85. Holtzer R, et al. Cognitive processes related to gait velocity: results from the Einstein Aging Study. *Neuropsychology*. 2006;20(2):215–23.
86. Holtzer R, Wang C, Verghese J. The relationship between attention and gait in aging: facts and fallacies. *Mot Control*. 2012;16(1):64–80.
87. Holtzer R, et al. The protective effects of executive functions and episodic memory on gait speed decline in aging defined in the context of cognitive reserve. *J Am Geriatr Soc*. 2012;60(11):2093–8.
88. Birnie K, et al. Childhood socioeconomic position and objectively measured physical capability levels in adulthood: a systematic review and meta-analysis. *PLoS One*. 2011;6(1):e15564.
89. Hurst L, et al. Lifetime socioeconomic inequalities in physical and cognitive aging. *Am J Public Health*. 2013;103(9):1641–8.
90. Russo A, et al. Lifetime occupation and physical function: a prospective cohort study on persons aged 80 years and older living in a community. *Occup Environ Med*. 2006;63(7):438–42.
91. Zaninotto P, Sacker A, Head J. Relationship between wealth and age trajectories of walking speed among older adults: evidence from the English Longitudinal Study of Ageing. *J Gerontol A Biol Sci Med Sci*. 2013;68(12):1525–31.
92. Sainio P, et al. Educational differences in mobility: the contribution of physical workload, obesity, smoking and chronic conditions. *J Epidemiol Community Health*. 2007;61(5):401–8.
93. Welmer AK, et al. Education-related differences in physical performance after age 60: a cross-sectional study assessing variation by age, gender and occupation. *BMC Public Health*. 2013;13:641.





# Epidemiology and Falls Risk Factors in Cognitively Impaired Older Adults

# 3

Stephanie A. Bridenbaugh and Reto W. Kressig

## Epidemiology of Falls

Falls are a common occurrence among older adults. The prevalence increases with age and the consequences can be devastating. The Prevention of Falls Network Europe (ProFANE) group defined a fall as “an unexpected event in which the participant comes to rest on the ground, floor or lower level” [1]. The medical and lay communities do not always have the same understanding of what constitutes a fall [2, 3]. Older fallers may underreport their falls or concerns about falling to caregivers and healthcare professionals for a number of reasons. Many perceive a fall as such only if it resulted in an injury [3]. Some older adults may see falls as an unavoidable consequence of aging, consider falls random events, or not recognize that they may be personally at risk for falling. Longer time intervals between a fall and being questioned about a fall lower recall of the fall. Cummings et al. showed in a 12-month prospective study of 304 ambulatory adults over the age of 60 that, depending on the time period of recall, 13–32% of those with confirmed falls did not recall falling during that time [4]. Additionally, those with cognitive impairment, as measured by lower scores on the Mini-Mental State Examination test, were more likely to forget falls than those with higher scores [4].

## Epidemiology of Falls in Older Adults

Among older adults living in the community, 30% of those aged 65 and older and 50% of those aged 80 and older fall each year [5, 6]. Older adults who have fallen in the previous 12 months have an increased risk of falling again (likelihood ratio range 2.3–2.8) [2]. Falls in older adults are associated with morbidity, mortality,

---

S. A. Bridenbaugh (✉) · R. W. Kressig  
University Department of Geriatric Medicine FELIX PLATTER, Basel, Switzerland  
e-mail: [stephanie.bridenbaugh@felixplatter.ch](mailto:stephanie.bridenbaugh@felixplatter.ch); [RetoW.Kressig@felixplatter.ch](mailto:RetoW.Kressig@felixplatter.ch)

poorer overall functioning, and early admission to long-term care facilities [7]. Recurrent falls are a common reason for long-term care facility admission in previously functionally independent older adults [8]. Approximately half of ambulatory residents of long-term care facilities fall at least once a year [7]. The mean fall incidence rate in long-term care facility residents is about three times the rate for community-dwelling older adults (mean 1.5 falls per bed annually) [8, 9]. In older hospitalized patients, fall rates vary from 3 to 20 per 1000 bed-days [2, 10]. Fall rates among institution-dwelling older adults may be more accurate than recall of community dwellers because of direct monitoring and reporting by staff [9].

## **Epidemiology of Falls in Cognitively Impaired Older Adults**

Both falls and cognitive impairment are common among older adults, and the prevalence of each increases with age. The annual incidence of falls in older adults with moderate to severe cognitive impairment is 60–80% [7, 11], at least twice the falls rate of cognitively healthy older adults [12]. In a Swedish study with just over 2000 cognitively impaired (assessed by the Multi-Dimensional Dementia Assessment Scale) residents (69% women, mean age 83.5 years) of geriatric care settings, almost 10% fell in the preceding week [13]. Older adults with dementia or cognitive impairment recover less well after a fall, have worse outcomes after treatment of fall-related fractures, and have higher mortality compared to cognitively healthy older adults [14, 15]. Older fallers with cognitive impairment are five times more likely to be institutionalized than non-fallers with cognitive impairment [16]. Since severely demented older adults, as well as the cognitively impaired oldest old, are underrepresented in studies, fall rates for these populations may be conservative [17].

### **Mild Cognitive Impairment**

The prevalence of mild cognitive impairment (MCI) is reported to be 17–19% in adults age 65 years and older and increases to 29% in those older than 85 years [18, 19]. Older adults with MCI develop Alzheimer's disease at a rate of 10–30% annually, whereas those without MCI develop dementia at a rate of 1–2% annually [18]. Compared to age-matched controls, older adults with MCI have a 10–15 times higher risk of developing Alzheimer's disease, as well as a higher risk of falling [19], as described in detail in Chap. 12.

### **Alzheimer's Dementia**

Alzheimer's dementia (AD) is the most common form of dementia and accounts for more than 50% of newly diagnosed dementia cases each year [20]. In Europe, the prevalence of AD is estimated at 5% (95% confidence interval (CI), 4.73–5.39) and the incidence at 11 per 1000 person-years (95% CI, 10.30–11.89) [21]. In the United States, 11% of people age 65 and older and 32% of people age 85 and older have AD [22]. One study reported that 42% of community-dwelling older adults (mean age 74 years) with mild to moderately severe AD fell during a 12-month period [20, 23].

### **Parkinson's Disease and Parkinson's Disease Dementia**

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and affects approximately 2% of adults age 65 years and older [24]. Increasing severity of motor impairment with progression of PD is associated with falls [24]. In a prospective study of 52 non-demented older adults with PD compared to 50 age- and sex-matched controls, those with PD fell more frequently, both with a single fall (PD 40%, controls 28%) and with recurrent falls (PD 29%, controls 12%) over the 12-month study period [24].

Cognitive impairment is common in PD, even in early stages of the disease, with a high risk of progression to dementia [24]. Parkinson's disease dementia (PDD) is defined as dementia starting 1 year or more after the diagnosis of PD. Up to 80% of older adults with PD develop PDD [25]. The risk of developing PDD increases with age and duration of PD, and the dementia incidence is approximately 100 per 1000 person-years [25]. Falls due to progressive gait and motor difficulties, postural instability, and progressive cognitive decline are common in PD and in PDD, but data are not conclusive regarding fall rates and fall-related injuries specifically in these populations. A detailed explanation of falls risk and outcomes in PD spectrum is described in Chap. 11.

### **Dementia with Lewy Bodies**

Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia in people older than 65 years and accounts for 10–25% of dementia cases [20, 26]. As with all dementias, gait and cognition worsen with disease progression. Studies show that the rate of annual cognitive decline is more rapid in DLB than in AD or PDD [26]. Disproportionate attentional, executive function and visual processing deficits are typical for DLB [27]; however, few data are available regarding subdomain-specific cognitive decline in DLB [26]. Spatial and perceptual difficulties begin early in the disease, as do hallucinations, sleep disturbances, and autonomic dysfunction and fluctuations in arousal, cognition, and attention [26, 27], all of which could increase the falls risk.

---

## **Falls Risk Factors**

Falls risk factors are generally categorized into those intrinsic (e.g., age, cognitive impairment, etc.) or extrinsic to the person (e.g., environment, footwear, etc.). The World Health Organization recommends four categories of falls risk factors in older adults: biological (e.g., age, gender, illnesses), behavioral (e.g., excess alcohol intake, lack of exercise), environmental (e.g., slippery floors, insufficient lighting), and socioeconomic (low income, low education levels). Division into these categories may aid recognition of modifiable risk factors that can be targeted by prevention or treatment strategies ([https://www.who.int/ageing/projects/falls\\_prevention\\_older\\_age/en/](https://www.who.int/ageing/projects/falls_prevention_older_age/en/) accessed 24 March 2019).

## Falls Risk Factors in Older Adults

The etiology of falls in older adults is often multifactorial, and the number of reported falls risk factors for older adults is large. The risk of falling increases with the number of falls risk factors present. Tinetti et al. reported in a 1-year prospective study of older community dwellers age 75 years or older that falls rates increased linearly from 8% for those with no risk factors to 78% for those with four or more risk factors [12]. Results were similar for institutionalized older adults [28]. A summary of falls risk factors identified in a univariate analysis of multiple risk factors from 16 studies (eight with community-dwelling and eight with institution-dwelling older adults) is shown in Table 3.1 [8, 29].

A *history of falling* is an independent risk factor for further falls in older adults, particularly after two or more falls in 1 year or an injurious fall [30]. In older adults with *symptoms of depression*, falls risk may be increased by 30% [31]. Additional falls risk factors not listed in Table 3.1 yet identified in other studies merit mention. *Recent hospitalization* increases the fall risk in older adults [32]. Falls risk in older adults is increased when *new prescription medications* are initiated and by the consumption of two or more classes of fall-related medications [30, 33, 34]. *Falls risk-increasing drugs* include cardiovascular agents ( $\alpha$ -blockers,  $\beta$ -blockers, calcium channel blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and vasodilators), central nervous system drugs (antipsychotics, sedative hypnotics, benzodiazepines, antidepressants and antiparkinsonians), analgesics (NSAIDs), thyroid drugs, and antidiabetics (biguanides, sulfonylureas, other oral hypoglycemic drugs, and insulin) [30, 35, 36].

## Falls Risk Factors in Cognitively Impaired Older Adults

There is a well-established association between cognition and falls. As cognitive capacities decline, gait and physical function worsen and the falls rate increases. Most falls risk factors are applicable to older adults in general, regardless of their

**Table 3.1** Risk factors for falls

Risk factor	Mean RR-OR <sup>a</sup>
Muscle weakness	4.4
History of falls	3.0
Gait deficit	2.9
Balance deficit	2.9
Use of assistive device	2.6
Visual deficit	2.5
Arthritis	2.4
Impaired activities of daily living	2.3
Depression	2.2
Cognitive impairment	1.8
Age > 80 years	1.7

<sup>a</sup>Relative risk ratios (RR) calculated for prospective studies, odds ratios (OR) calculated for retrospective studies

cognitive status, yet only few falls risk factors specific to cognitive impairment, dementia, or dementia subtypes have been identified. A recent systematic review identified falls risk factors unique to older adults (community- as well as institution-dwelling) with dementia: verbally disruptive and attention-seeking behavior, cortical changes on imaging studies, visual perception problems, and caregiver burden [17].

Although there is a clear association between cognitive impairment and falls, the mechanisms underlying this association are less clear. Some difficulties in interpreting the data on falls risk factors in cognitively impaired older adults is due to the heterogeneity of the populations studied, the severity of the cognitive impairment, as well as the methods used to assess cognition. For example, some tests, such as the Mini-Mental State Examination (MMSE), evaluate global cognition but do not assess specific cognitive domains such as executive function. Executive dysfunction, also detected by slow, irregular gait tested under dual-task conditions, is associated with an increased falls risk. Even among healthy older adults with “normal” cognition as determined by MMSE scores, low performance in executive function was prospectively associated with falls [37]. The latter challenges the concept of “normal” cognition and poses the question of when to implement preventive and therapeutic measures for both cognitive decline and falls.

Cognitive domains that have been repeatedly identified as falls risk factors across the spectrum of cognitive impairments are slow processing speed, attention deficits, and executive dysfunction (see Table 3.2). Neural pathways shared by these cognitive domains and the neuromotor control of gait may be disrupted in cognitive decline, causing deficits in gait control, thus increasing the falls risk. A lack of insight or awareness of one’s own cognitive and physical functional abilities and/or executive dysfunction decreasing inhibitory control may lead to task-inappropriate behavior, also increasing the falls risk [38]. Systematic reviews have shown a relationship between executive dysfunction and falls, and a meta-analysis of 27 prospective cohort studies showed that executive dysfunction doubled the risk of future falls and increased the risk of serious injury by 40% in community-dwelling older adults [38].

During ambulation, particularly under challenging environmental or dual-task situations, cognitively healthy older adults instinctively adopt a “posture first” strategy, prioritizing safe posture and balance. Cognitively impaired older adults, however, tend to adopt a “cognition first” or, rather, a “posture second” strategy, prioritizing a cognitive task above stable gait and posture, thus increasing their risk for falls [38]. Interventions to improve mobility and cognition may aim to re-establish the safer “posture first” strategy.

Physical and cognitive functions are strongly interrelated in aging, and deficits in each are independent risk factors for falling in older adults [7]. Studies suggest that cognitive impairment amplifies the effect of physical deficits on injurious falls [39, 40]. Deficits in specific cognitive domains such as attention, executive function, and processing speed are associated with an increased falls risk for older adults [37, 39, 40]. A population-based study on almost 2500 Swedish adults aged 60 years or older reported that each standard deviation worsening in processing speed, and executive function was significantly associated with a 10% increased risk of

**Table 3.2** Falls risk factors in older adults

In general	Cognitive impairment in general	Mild cognitive impairment	Dementia in general	Dementia subtypes
	Slowed processing speed Attention deficits	Difficulties with problem-solving Impaired spatial awareness Decreased gray matter volume	Verbally disruptive behavior Attention-seeking behavior Cortical changes in neuroimaging Visual perception problems Caregiver burden	Disease-specific, such as worsening gait and balance, retropulsion and freezing of gait in Parkinson's disease
<b>Intrinsic / biological</b> e.g. muscle weakness, falls history, balance deficits, impaired vision/hearing, vertigo/dizziness, chronic illness, depression, cognitive impairment, impaired ADL <sup>a</sup> , age > 80 years				
<b>Extrinsic/ environmental</b> e.g. insufficient lighting, slippery floors, uneven ground, use of walking aid, recent hospitalization, new medications, fall risk-increasing drugs				
<b>Socio-economic</b> e.g., low level of education, low income, limited access to health, social and community services				
<b>Behavioral</b> e.g. alcohol/drug abuse, lack of exercise, inappropriate footwear, task inappropriate behavior				
<b>Gait</b> e.g. slowed walking speed, increased stride-to-stride variability, particularly under dual task conditions				
<b>Executive dysfunctions</b> measured by neuropsychological assessments and/or spatiotemporal gait analysis under dual task conditions				

The authors propose that falls risk factors for older adults in general apply to those with cognitive impairment as well, although with progressive cognitive decline, disease-specific falls risk factors (not yet completely identified) may dominate; the fading of the color bar from left to right in the table represents this. Gait impairments and executive dysfunction increase as cognition worsens, and their presence in older adults with “normal” cognition likely represents early detection of or risk factors for cognitive deficits and falls; this is represented by the fading of the color bar from right to left.

<sup>a</sup>ADL activities of daily living

injurious falls over 10 years [40]. Studies also suggest that slow processing speed, attention impairments, and poor executive function may be early signs not only of cognitive impairment but also of declining physical function, thus increasing the falls risk [37, 40–42].

It is a clinical challenge to know which risk factors carry the most weight in terms of clinical relevance for a certain type of cognitive impairment, thus knowing where to direct preventive, diagnostic, and therapeutic measures. Falls risk factors identified in the literature for certain types of cognitive impairment are described briefly below. Table 3.2 summarizes this information and combines it with falls risk factors identified for older adults in general, categorizing them into not only intrinsic and extrinsic factors but also according to the four falls risk categories proposed by the WHO [29] ([https://www.who.int/ageing/projects/falls\\_prevention\\_older\\_age/en/](https://www.who.int/ageing/projects/falls_prevention_older_age/en/) accessed 24 March 2019).

### **Mild Cognitive Impairment**

Older adults with MCI have impairments in gait, balance, and executive function, which are independent risk factors for falls [18]. Attention deficits and slowed psychomotor processing as well as impairments in problem-solving and spatial awareness are associated not only with MCI but also with balance control and falls [18, 43]. Liu-Ambrose et al. reported that Canadian community-dwelling women age 65–75 years with MCI had greater postural sway, worse executive functions, and a higher risk of falling than those without MCI [18]. A study with magnetic resonance imaging on 42 older adults with MCI (43% women, mean age 75.6 years) identified an association between falls and cerebral gray matter volume [44]. Compared to non-fallers, fallers had lower gray matter volume in the bilateral middle frontal gyrus and superior frontal gyrus, corresponding to the premotor cortex and supplementary motor area [44]. The authors suggested that these regions may be associated with falls because the middle frontal gyrus is involved in controlling behavior with spatial and sensory guidance [44].

### **Alzheimer's Dementia**

Compared to older adults with healthy cognition, those with mild to moderately severe Alzheimer's dementia have impaired static and dynamic balance with increased reliance on vision for balance control, contributing to the increased falls risk in this population [20, 45]. Older adults with mild to moderately severe AD also have difficulties turning (increased turn time and sway compared to cognitively healthy older adults), which may also increase their falls risk [20].

### **Parkinson's Disease and Parkinson's Disease Dementia**

PD-specific risk factors are significantly associated with an increased risk of multiple falls, namely, cognitive impairment, prior falls, the Hoehn and Yahr score (for staging of motor function), and freezing of gait [24]. Further falls risk factors specific to PD or PDD have not been identified, though features such as orthostatic blood pressure change and dyskinesias may contribute to increased falls risk.



## Dementia with Lewy Bodies

Many of the physical, cognitive, and behavioral symptoms of DLB (see section “[Dementia with Lewy Bodies](#)”) are independent falls risk factors for older adults in general as well as those with cognitive impairment. Scarce data are available regarding DLB-specific falls risk factors and falls rates; however, the progressive cognitive, behavioral, autonomic, and motor deficits accompanying DLB suggest high fall rates in this population.

## Gait Changes as a Predictor of Cognitive Impairment and of Falls

Older adults with gait deficits have an increased risk of developing cognitive deficits, and, in turn, cognitive deficits are associated with worsened gait [46]. Both gait impairments and cognitive impairments are risk factors for falls in older adults [47]. Quantitative spatiotemporal gait impairments, particularly slowed gait speed and increased gait irregularity, are associated with an increased falls risk across the spectrum of cognitive impairment (see Table 3.2) [38].

One specific early change in gait performance in cognitively impaired older adults is slowed walking speed [38]. A safe, normal walking speed for older adults is at least 1 m/s. Those who walk slower have an increased incidence of falls, hospitalization, disability, and institutionalization compared to people of the same age with a normal walking speed [48]. Burrachio et al. showed in a retrospective analysis of 204 older adults with initially normal cognition that an accelerated slowing of walking speed preceded diagnosis of MCI by up to 12 years [49]. Recently, the concept of motoric cognitive risk syndrome was introduced, in which the presence of subjective complaints of cognition and slower gait in older adults are better predictors of developing dementia than either subjective cognitive complaints or slow gait alone [50].

Gait variability (stride-to-stride changes in length or time of a given gait parameter) is recognized as a sensitive marker of higher-level brain control of gait [38, 51]. Variability is a marker of gait automaticity, with low variability representing regular, stable gait [51]. Normal fluctuations in stride time variability are usually below 3% in healthy older adults [38]. As cognition worsens, gait speed slows and stride time variability increases [52]. High stride time variability has been shown to predict falls in community-dwelling older adults, even when gait velocity did not distinguish fallers from non-fallers [19].

Gait slowing and high stride time variability are associated with deficits in executive functions [19]. Executive functions are responsible for planning and coordinating complex processes, placing task events in the correct order, and dividing attention among simultaneously performed tasks. Impaired executive function, but not memory impairment, has been associated with an increased fall prevalence in older adults [53]. In 1997, Lundin-Olsson et al. showed in a landmark paper that “stops walking when talking” is associated with an increased falls risk in older adults [54]. That observation highlighted the clinical significance of dual-task test



paradigms. The dual-task paradigm examines the effect of a simultaneously performed motor or cognitive task on gait performance. The dual-task paradigm can be thought of as a cognitive stress resistance test to detect deficits of motor-gait control and falls risk, which under the single-task condition of walking alone may otherwise remain undetected, particularly in the early stages of cognitive impairment [38, 48, 51]. The change in someone's gait performance from a single task to a dual task is termed the dual-task cost. Increased dual-task costs are greater in older than in younger adults, in fallers than in non-fallers, and in cognitively impaired than in cognitively healthy older adults [51].

In summary, there is a well-established association between gait, cognition, and falls in older adults. Slowed gait speed and increased stride-to-stride variability, particularly under dual-task conditions, are falls risk predictors across the spectrum of cognition and are associated with executive dysfunction. Quantifying gait should be an integral component of geriatric assessment for early detection of cognitive deficits and falls risk. Early detection allows early implementation of interventions to prevent falls and fall-related injuries.

---

## Fall-Related Injuries

### Fall-Related Injuries in Older Adults

Falls occur at all ages, particularly among children and athletes, but older adults are more susceptible to fall-related injuries [8]. Injurious falls are associated with increased risk of hospitalization, functional dependence, reduced quality of life, and premature death [39, 55]. In fact, 75% of deaths due to falls in the United States occur in the population of adults 65 years and older [8].

Falls are the leading cause of fatal and nonfatal injuries among adults aged 65 years and older [56]. 30–50% of falls result in minor lesions such as bruises or lacerations; however, 5–10% of falls result in a fracture or traumatic head injury [2, 29, 57]. In older fallers aged 65–75 years, wrist fractures are more common than hip fractures; whereas, in those older than 75 years, hip fractures are the most common fall-related fracture, likely reflecting slowed reaction times and the loss of ability to extend the arms quickly enough to “break” a fall [58]. Ninety percent of all hip fractures in older adults are due to falls [2, 57]. In the year following a hip fracture, one-fourth of the older fallers will die [59], 76% will have worsened mobility [60], 50% will have difficulties performing their activities of daily living [59], and 22% will be admitted to a nursing home [2, 60].

Falling without serious injury increases the risk of skilled nursing facility placement threefold after accounting for cognitive, psychological, social, functional, and medical factors; a serious fall injury increases the risk tenfold [61]. About half of older fallers are unable to get up on their own, with the lie time resulting in medical conditions such as dehydration, hypothermia, pressure sores, and rhabdomyolysis [2, 62].

## Fall-Related Injuries in Cognitively Impaired Older Adults

Compared to cognitively healthy older adults, those with cognitive impairment not only fall more often but also sustain more serious fall-related injuries such as fractures and head injuries, which also increase the risk of mortality [37]. Compared to those who are cognitively healthy, older adults with cognitive impairment are less likely to make a good functional recovery after a fall-related injury [15]. Currently, little is known about fall-related injuries specific to deficits in certain cognitive domains, cognitive impairment in general, or dementia subtypes. Muir and Montero-Odasso found in a systematic review and meta-analyses that cognitive impairment increases the risk of injuries after a fall at least three times when compared with cognitive-intact populations.

---

## Fear of Falling

In addition to physical injuries, falls can have negative psychosocial complications, such as fear of falling, which can cause older fallers to limit their activities, leading to reduced mobility, deconditioning and increased falls risk [46, 63, 64]. Fear of falling can also lead to activity avoidance, social isolation, and depression [8, 65, 66]. A fear of falling can be present in older non-fallers as well. In community-dwelling older adults, prevalence rates for fear of falling range from 20% to 85% [65, 67]. Variables associated with fear of falling include age 80 years and older, female gender, fair and poor perceived general health, and having one or more falls [65]. In older adult residents of a senior living facility with at least one fall in the previous year and no significant cognitive impairment (Mini-Mental State Examination scores of 24 points or greater), fear of falling was greater among those who were depressed, walked slowly (habitual walking speed less than 90 cm/s), and used a walking aid [68].

Studies suggest that older adults with cognitive impairment often have less fear of falling than cognitively healthy adults and that the fear of falling decreases as cognitive impairment worsens [67, 69–71]. A possible explanation is anosognosia for neuropsychological deficits as well as limited insight into declining physical function and a personal risk of falling [67]. This, in turn, may prevent affected older adults from adopting safe strategies during transfer and ambulation, which may increase the falls risk [67].

Uemura et al. found that memory decline was associated with a lower prevalence of fear of falling in community-dwelling older adults [71]. The same authors reported that older adults with global cognitive impairment had a lower prevalence of fear of falling than those with mild cognitive impairment [70]. De Borges et al. found that older adults with Alzheimer's disease were less fearful than those with mild cognitive impairment [69]. More recently, Shirooka et al. investigated fear of falling in 483 community dwellers age 65 years or older with cognitive impairment (Mini-Mental State Examination Score of 26 points or less from maximum of 30; higher scores represent better cognition). The study population was divided into frail and non-frail cohorts (based on findings from the Cardiovascular Health Study). The authors reported that in frail older adults, cognitive impairment was significantly associated with an absence of fear of falling, even after adjusting for demographic factors such

as age, sex, body mass index, and educational history [67]. Cognitive impairment was not associated with fear of falling in the non-frail older adults [67].

It is important to understand concerns of caregivers of older fallers. Caregivers fear not only the immediate consequences of their carees' falls but also about future falls, quality of life, and survival [72]. Some carers injure themselves while trying to prevent their caree from falling and/or when helping their caree get up after a fall [72]. Many caregivers experience an increased burden of care after a caree falls, including constant worry and vigilance, changes in home and work routines, social withdrawal because of reluctance to leave the caree home alone, low self-rated health, and poorer quality of life [72].

---

## Socioeconomic Impact of Falls

In a World Health Organization document from 2002 entitled, "Active Aging: a Policy Framework," authors posed this question, which is still relevant: How do we best balance the role of the family and the state when it comes to caring for people who need assistance, as they grow older?

Costs associated with falls in older adults are substantial. In addition to indirect costs and caregiver burden (including sick days as well as presenteeism), the direct costs of emergency, acute, rehabilitation, and long-term care are an increasing challenge for healthcare systems [37]. In the US population of adults age 65 years and older in the year 2015, the estimated medical costs attributable to fatal and nonfatal falls were approximately \$50 billion, and the overall medical spending for fatal falls was estimated to be \$754 million [73]. Direct costs from fall-related injuries account for up to 1.5% of healthcare costs in European countries (this does not include the indirect costs, such as loss of income to fallers and the caregivers) [2].

With an ever-increasing population of older adults, particularly of the oldest old, the number of falls, fall-related injuries, hospitalizations, and institutionalizations will rise accordingly. This trend will be accompanied by an ever-increasing burden for individuals, families, and the society and is a major public health concern. It is crucial that falls risk is identified in both cognitively healthy and in cognitively impaired older adults and that interventions to treat and prevent falls are implemented as soon as possible to keep the socioeconomic burden as low as possible while keeping the quality of life and functional independence for each older adult as high as possible.

---

## References

1. Lamb SE, Jorstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. *J Am Geriatr Soc.* 2005;53(9):1618–22.
2. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. *Maturitas.* 2013;75(1):51–61.
3. Zecevic AA, Salmoni AW, Speechley M, Vandervoort AA. Defining a fall and reasons for falling: comparisons among the views of seniors, health care providers, and the research literature. *Gerontologist.* 2006;46(3):367–76.

4. Cummings SR, Nevitt MC, Kidd S. Forgetting falls. The limited accuracy of recall of falls in the elderly. *J Am Geriatr Soc.* 1988;36(7):613–6.
5. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil.* 2001;82(8):1050–6.
6. Inouye SK, Brown CJ, Tinetti ME. Medicare nonpayment, hospital falls, and unintended consequences. *N Engl J Med.* 2009;360(23):2390–3.
7. Kenny RA, Rubenstein LZ, Tinetti ME, et al. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc.* 2011;59(1):148–57.
8. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* 2001;49(5):664–72.
9. Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. *Ann Intern Med.* 1994;121(6):442–51.
10. Vassallo M, Azeem T, Pirwani MF, Sharma JC, Allen SC. An epidemiological study of falls on integrated general medical wards. *Int J Clin Pract.* 2000;54(10):654–7.
11. Shaw FE. Prevention of falls in older people with dementia. *J Neural Transm (Vienna).* 2007;114(10):1259–64.
12. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* 1988;319(26):1701–7.
13. Kallin K, Gustafson Y, Sandman PO, Karlsson S. Factors associated with falls among older, cognitively impaired people in geriatric care settings: a population-based study. *Am J Geriatr Psychiatry.* 2005;13(6):501–9.
14. Harlein J, Dassen T, Halfens RJ, Heinze C. Fall risk factors in older people with dementia or cognitive impairment: a systematic review. *J Adv Nurs.* 2009;65(5):922–33.
15. Shaw FE. Falls in cognitive impairment and dementia. *Clin Geriatr Med.* 2002;18(2):159–73.
16. Myers AH, Baker SP, Van Natta ML, Abbey H, Robinson EG. Risk factors associated with falls and injuries among elderly institutionalized persons. *Am J Epidemiol.* 1991;133(11):1179–90.
17. Fernando E, Fraser M, Hendriksen J, Kim CH, Muir-Hunter SW. Risk factors associated with falls in older adults with dementia: a systematic review. *Physiother Can.* 2017;69(2):161–70.
18. Liu-Ambrose TY, Ashe MC, Graf P, Beattie BL, Khan KM. Increased risk of falling in older community-dwelling women with mild cognitive impairment. *Phys Ther.* 2008;88(12):1482–91.
19. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil.* 2012;93(2):293–9.
20. Suttanon P, Hill KD, Said CM, Logiudice D, Lautenschlager NT, Dodd KJ. Balance and mobility dysfunction and falls risk in older people with mild to moderate Alzheimer disease. *Am J Phys Med Rehabil.* 2012;91(1):12–23.
21. Niu H, Alvarez-Alvarez I, Guillen-Grima F, Aguinaga-Ontoso I. Prevalence and incidence of Alzheimer's disease in Europe: a meta-analysis. *Neurologia.* 2017;32(8):523–32.
22. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2016;12(4):459–509.
23. Horikawa E, Matsui T, Arai H, Seki T, Iwasaki K, Sasaki H. Risk of falls in Alzheimer's disease: a prospective study. *Intern Med.* 2005;44(7):717–21.
24. Camicioli R, Majumdar SR. Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-Year Prospective Cohort Study. *Gait Posture.* 2010;32(1):87–91.
25. Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. *Lancet.* 2015;386(10004):1683–97.
26. Mueller C, Ballard C, Corbett A, Aarsland D. The prognosis of dementia with Lewy bodies. *Lancet Neurol.* 2017;16(5):390–8.
27. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology.* 2017;89(1):88–100.

28. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. *Am J Med.* 1986;80(3):429–34.
29. Rubenstein LZ, Josephson KR. The epidemiology of falls and syncope. *Clin Geriatr Med.* 2002;18(2):141–58.
30. Bolding DJ, Corman E. Falls in the geriatric patient. *Clin Geriatr Med.* 2019;35(1):115–26.
31. Hoffman GJ, Hays RD, Wallace SP, Shapiro MF, Ettner SL. Depressive symptomatology and fall risk among community-dwelling older adults. *Soc Sci Med.* 2017;178:206–13.
32. Hill AM, Hoffmann T, Beer C, McPhail S, Hill KD, Oliver D, et al. Falls after discharge from hospital: is there a gap between older peoples' knowledge about falls prevention strategies and the research evidence? *The Gerontologist.* 2011;51(5):653–62.
33. Musich S, Wang SS, Ruiz J, Hawkins K, Wicker E. Falls-related drug use and risk of falls among older adults: a study in a US medicare population. *Drugs Aging.* 2017;34(7):555–65.
34. Zia A, Kamaruzzaman SB, Tan MP. The consumption of two or more fall risk-increasing drugs rather than polypharmacy is associated with falls. *Geriatr Gerontol Int.* 2017;17(3):463–70.
35. Bloch F, Thibaud M, Tournoux-Facon C, Breque C, Rigaud AS, Dugue B, et al. Estimation of the risk factors for falls in the elderly: can meta-analysis provide a valid answer? *Geriatr Gerontol Int.* 2013;13(2):250–63.
36. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* 2009;169(21):1952–60.
37. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc.* 2012;60(11):2127–36.
38. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: implications for risk assessment and prevention. *J Am Geriatr Soc.* 2018;66(2):367–75.
39. Ek S, Rizzuto D, Fratiglioni L, Johnell K, Xu W, Welmer AK. Risk profiles for injurious falls in people over 60: a population-based cohort study. *J Gerontol A Biol Sci Med Sci.* 2018;73(2):233–9.
40. Welmer AK, Rizzuto D, Laukka EJ, Johnell K, Fratiglioni L. Cognitive and physical function in relation to the risk of injurious falls in older adults: a population-based study. *J Gerontol A Biol Sci Med Sci.* 2017;72(5):669–75.
41. Ward RE, Quach L, Welch SA, Leveille SG, Leritz E, Bean JF. Interrelated neuromuscular and clinical risk factors that contribute to falls. *J Gerontol A Biol Sci Med Sci.* 2019; Feb 5. <https://doi.org/10.1093/gerona/glz030>. [Epub ahead of print].
42. Tyrovolas S, Koyanagi A, Lara E, Santini ZI, Haro JM. Mild cognitive impairment is associated with falls among older adults: findings from the Irish Longitudinal Study on Ageing (TILDA). *Exp Gerontol.* 2016;75:42–7.
43. Alexander NB, Hausdorff JM. Guest editorial: linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci.* 2008;63(12):1325–8.
44. Makizako H, Shimada H, Doi T, Park H, Yoshida D, Uemura K, et al. Poor balance and lower gray matter volume predict falls in older adults with mild cognitive impairment. *BMC Neurol.* 2013;13:102.
45. Leandri M, Cammisuli S, Cammarata S, Baratto L, Campbell J, Simonini M, et al. Balance features in Alzheimer's disease and amnesic mild cognitive impairment. *J Alzheimers Dis.* 2009;16(1):113–20.
46. Bridenbaugh SA, Kressig RW. Laboratory review: the role of gait analysis in seniors' mobility and fall prevention. *Gerontology.* 2011;57(3):256–64.
47. Montero-Odasso M, Wells JL, Borrie MJ, Speechley M. Can cognitive enhancers reduce the risk of falls in older people with mild cognitive impairment? A protocol for a randomised controlled double blind trial. *BMC Neurol.* 2009;9:42.
48. Bridenbaugh SA, Kressig RW. Motor cognitive dual tasking: early detection of gait impairment, fall risk and cognitive decline. *Z Gerontol Geriatr.* 2015;48(1):15–21.
49. Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J. The trajectory of gait speed preceding mild cognitive impairment. *Arch Neurol.* 2010;67(8):980–6.
50. Verghese J, Annweiler C, Ayers E, Barzilai N, Beauchet O, Bennett DA, et al. Motoric cognitive risk syndrome: multicountry prevalence and dementia risk. *Neurology.* 2014;83(8):718–26.

51. Bridenbaugh SA, Kressig RW. Quantitative gait disturbances in older adults with cognitive impairments. *Curr Pharm Des.* 2014;20(19):3165–72.
52. Bridenbaugh SA. How does gait change as cognitive decline progresses in the elderly? *Alzheimers Dement.* 2012;8(4):131–2.
53. Allali G, Launay CP, Blumen HM, Callisaya ML, De Cock AM, Kressig RW, et al. Falls, cognitive impairment, and gait performance: results from the GOOD initiative. *J Am Med Dir Assoc.* 2017;18(4):335–40.
54. Lundin-Olsson L, Nyberg L, Gustafson Y. “Stops walking when talking” as a predictor of falls in elderly people. *Lancet.* 1997;349(9052):617.
55. Alexander BH, Rivara FP, Wolf ME. The cost and frequency of hospitalization for fall-related injuries in older adults. *Am J Public Health.* 1992;82(7):1020–3.
56. Bergen G, Stevens MR, Burns ER. Falls and fall injuries among adults aged  $\geq 65$  years – United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2016;65(37):993–8.
57. Goldacre MJ, Roberts SE, Yeates D. Mortality after admission to hospital with fractured neck of femur: database study. *BMJ.* 2002;325(7369):868–9.
58. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age Ageing.* 2006;35 Suppl 2:ii37–41.
59. Abdelhafiz AH, Austin CA. Visual factors should be assessed in older people presenting with falls or hip fracture. *Age Ageing.* 2003;32(1):26–30.
60. March LM, Chamberlain AC, Cameron ID, Cumming RG, Brnabic AJ, Finnegan TP, et al. How best to fix a broken hip. Fractured Neck of Femur Health Outcomes Project Team. *Med J Aust.* 1999;170(10):489–94.
61. Tinetti ME, Kumar C. The patient who falls: “It’s always a trade-off”. *JAMA.* 2010;303(3):258–66.
62. Fleming J, Brayne C. Inability to get up after falling, subsequent time on floor, and summoning help: prospective cohort study in people over 90. *BMJ.* 2008;337:a2227.
63. Dellinger AM, Stevens JA. The injury problem among older adults: mortality, morbidity and costs. *J Saf Res.* 2006;37(5):519–22.
64. Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ. Fear of falling and restriction of mobility in elderly fallers. *Age Ageing.* 1997;26(3):189–93.
65. Zijlstra GA, van Haastregt JC, van Eijk JT, van Rossum E, Stalenhoef PA, Kempen GL. Prevalence and correlates of fear of falling, and associated avoidance of activity in the general population of community-living older people. *Age Ageing.* 2007;36(3):304–9.
66. Soriano TA, DeCherrie LV, Thomas DC. Falls in the community-dwelling older adult: a review for primary-care providers. *Clin Interv Aging.* 2007;2(4):545–54.
67. Shirooka H, Nishiguchi S, Fukutani N, Tashiro Y, Nozaki Y, Hirata H, et al. Cognitive impairment is associated with the absence of fear of falling in community-dwelling frail older adults. *Geriatr Gerontol Int.* 2017;17(2):232–8.
68. Kressig RW, Wolf SL, Sattin RW, O’Grady M, Greenspan A, Curns A, et al. Associations of demographic, functional, and behavioral characteristics with activity-related fear of falling among older adults transitioning to frailty. *J Am Geriatr Soc.* 2001;49(11):1456–62.
69. Borges Sde M, Radanovic M, Forlenza OV. Fear of falling and falls in older adults with mild cognitive impairment and Alzheimer’s disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn.* 2015;22(3):312–21.
70. Uemura K, Shimada H, Makizako H, Doi T, Tsutsumimoto K, Yoshida D, et al. Effects of mild and global cognitive impairment on the prevalence of fear of falling in community-dwelling older adults. *Maturitas.* 2014;78(1):62–6.
71. Uemura K, Shimada H, Makizako H, Yoshida D, Doi T, Tsutsumimoto K, et al. A lower prevalence of self-reported fear of falling is associated with memory decline among older adults. *Gerontology.* 2012;58(5):413–8.
72. Ang SGM, O’Brien AP, Wilson A. Carers’ concerns about their older persons (Carees) at risk of falling – a mixed-methods study protocol. *BMC Health Serv Res.* 2018;18(1):819.
73. Florence CS, Bergen G, Atherly A, Burns E, Stevens J, Drake C. Medical costs of fatal and nonfatal falls in older adults. *J Am Geriatr Soc.* 2018;66(4):693–8.

# Depression, Fear of Falling, Cognition and Falls

# 4

Ryota Sakurai and Yoshiro Okubo

## Depression and Falls

Depression in older adults is a major mental health issue which increases risk of falling and bone fractures and negatively affects the process of regaining mobility following surgical operations [1, 2]. Depression can also be induced by recurrent falls, subsequent activity restriction and reduced social participation [3], creating a vicious circle of depression, poor health and falls in older people [1].

## Prevalence and Risk Factors for Depression

Prevalence of major and minor depression in older adults ranges from 1.4% to 12.4% and from 12.9% to 35%, respectively [4]. This variability in the range of prevalence depends on the criteria utilized and the study population targeted. One-year prevalence of major depression among 607,520 residents in the United States in 2015 was 7.3% and has increased over the past 10 years (6.6% in 2005) [5]. Prevalence of depression in 3056 Dutch adults aged 55–85 years old was 15% (2.02% major depression and 12.9% minor depression) [6]. Depression is more prevalent in certain age (young > middle aged > older adults), race and ethnicity (white > other > Hispanic > black), gender (women > men) and economic status (lower > higher income) [5]. However, in the Dutch population, prevalence of

---

R. Sakurai (✉)

Research Team for Social Participation and Community Health, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

e-mail: [sakurair@tmig.or.jp](mailto:sakurair@tmig.or.jp)

Y. Okubo

Falls, Balance and Injury Research Centre, Neuroscience Research Australia, Randwick, NSW, Australia

UNSW Sydney, Sydney, NSW, Australia

e-mail: [y.okubo@neura.edu.au](mailto:y.okubo@neura.edu.au)

© Springer Nature Switzerland AG 2020

M. Montero-Odasso, R. Camicioli (eds.), *Falls and Cognition in Older Persons*, [https://doi.org/10.1007/978-3-030-24233-6\\_4](https://doi.org/10.1007/978-3-030-24233-6_4)



depression significantly increased with advanced age (60–64 years, 11.5%, to 80–85 years, 19.4%) [6]. Risk factors for depression include stressful life events, insomnia, cardiovascular disease, loss of social roles and activity restriction [7].

## Assessments of Depression

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), defines major depression when an individual has at least five of the following nine symptoms for a period of at least 2 weeks: (i) depressed mood, (ii) loss of interest or pleasure in nearly all activities, (iii) changes in appetite or weight, (iv) sleep impairment, (v) psychomotor agitation (e.g. anxiety), (vi) fatigue, (vii) feelings of worthlessness or guilt, (viii) diminished ability to think, concentrate or make decisions or (ix) recurrent thoughts of death, suicidal ideation, plans or attempts [8]. While diagnosis of depression requires trained clinicians, there are many self-administered screening tools for depression commonly used in research and that are useful in practice [9, 10].

The Center for Epidemiologic Depression Scale (CES-D) developed by Radloff (1977) is a self-report scale to measure depressive symptoms in different ages [11]. The 20-item CES-D provides scores ranging from 0 to 60 with  $\geq 16$  as a cut point to indicate depression. CES-D has a sensitivity of 80% and a specificity of 73% for detecting clinically significant depression [12].

The Geriatric Depression Scale (GDS) introduced by Brink et al. (1982) is a self-rating, 30-item screening tool for depression particularly in older age [13]. The GDS has been standardized for community-dwelling older adults [14] including those with neurological conditions such as dementia [15], polio [16] and spinal cord injury [17]. The GDS short version with 15 items has also been shown to have similar reliability, validity, sensitivity and specificity as the long 30-item version [14, 15].

The Patient Health Questionnaire (PHQ) introduced by Spitzer et al. (1999) is also a self-administered instrument but designed according to the DSM-IV diagnostic criteria for depression [8, 18, 19]. The PHQ has a sensitivity of 73% and a specificity of 98% for detecting depression that is diagnosed by mental health professionals [19]. Nease et al. (2003) reviewed the accuracy and ease of the administration of screening tools and reported the 9-item PHQ to be the best available depression screening tool for primary care [9].

## Depression and Falls

Depression has been shown to increase the risk of future falls in prospective cohort studies [20–22]. Among 763 residents in Boston aged 70 and older, baseline depression significantly increased the risk of indoor and outdoor falls [20]. Among 529 community-dwelling older adults in Sydney, depressive symptoms and orthostatic hypotension increased the risk of unexplained falls (e.g. blackout, dizziness or feeling faint) [23]. In a sample of 472 long-term-care residents in southern Germany,



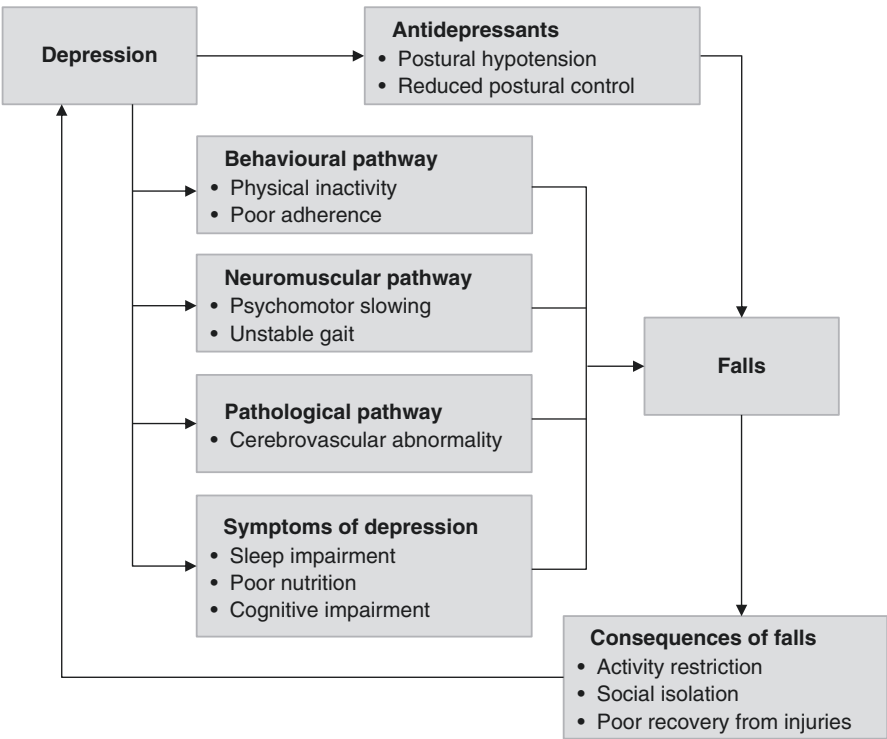
depressive symptoms, transfer assistance, urinary incontinence and fall history were associated with frequent falls [24]. A meta-analysis summarized the findings of 17 prospective studies and found that depression significantly increased risk of falls by 63% [25].

Mechanisms of How Depression May Lead to Falls

The mechanisms of the relationship between depression and falls are multifactorial, complex and bidirectional and are not completely understood. However, depression may lead to an increased risk of falls through behavioural, neuromuscular or pathological mechanisms (Fig. 4.1).

Behavioural Mechanisms

Depressed older adults generally have lower physical activity levels compared to those without depression [26]. Lee et al. (2017) examined temporal interrelationships between falls, physical activity and depressive symptoms in a cohort of post-hospitalized older adults and reported that depressive symptoms and low physical



**Fig. 4.1** Schematic diagram of the complex and bidirectional association between depression and falls

activity levels preceded falls [27]. Moreover, a lower sense of self-efficacy and negative expectations of the future in repeated fallers with depression can lead to decreased social participation [3]. Physical and social inactivity in depressed older adults may be a manifestation of deeper deteriorated mental and physical health that more directly increases the risk of falling. It is possible that social isolation and physical inactivity in depressed older adults may cause muscle weakness resulting in increased risk of falls.

Another behavioural pathway among severely depressed persons is poor adherence to prescribed medication [28], healthy diet, exercise and stress management [28]. Berry et al. (2010) found that low medication adherence (i.e. stop taking medication when feeling better or worse) in older adults was associated with a 50% increased rate of falls compared with high medication adherence [29].

### **Neuromuscular Mechanisms**

Psychomotor slowing, a common feature of major depression, can lead to impaired concentration to identify fall hazards and gait instability. For example, individuals with depression tend to walk slowly with a shorter stride length, longer standing phase, larger lateral body swing and increased gait variability [30, 31], all of which are established gait risk factors for falls [32, 33].

Kvelde et al. (2010) reported that depressed retirement village residents had slow choice stepping reaction time, a composite measure of fall risk [34, 35]. Moreover, the association between depression and slow choice stepping reaction time was mediated by quadriceps strength, executive function, simple reaction time and balance [34].

### **Pathological Mechanisms**

Neurobiological theories of depression include deficiency of monoamine, dysfunction of specific brain regions and impaired circadian rhythms [36, 37]. The monoamine-deficiency theory posits that a depletion of the neurotransmitters such as serotonin and norepinephrine in the brain underlies depression [36]. Antidepressants targeting to increase serotonin concentration improve mood, verbal memory, verbal fluency and psychomotor speed [38, 39].

Brain neuroimaging studies suggest the presence of abnormalities in frontal regions (e.g. anterior cingulate, prefrontal cortex) in major depression [37, 40]. The frontal cortex and executive function, involved in planning, control and execution of movements, are likely associated with increased risk of falls [41–43].

The “vascular depression” hypothesis posits that cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes [44]. Vascular depression is a subtype of depression characterized by late-onset ( $\geq 65$  years), cerebrovascular abnormality (e.g. white matter lesions) and impairment in executive function [44–46]. These traits are associated with poor antidepressant treatment responses [44, 45] and impairment in gait and mobility [46, 47].

## Mechanisms Through Symptoms of Depression

Sleep disorders such as insomnia and hypersomnia are symptoms of depression [8]. Stone et al. (2008) studied 2978 older women and reported that short night time sleep duration and increased sleep fragmentation were associated with increased risk of falls in older women, even when controlling for the use of sedatives [48]. Stone et al. (2014) also followed up 3101 older men and reported that excessive daytime sleepiness, short sleep duration (<5 h) and nocturnal hypoxemia were associated with greater risk of falls [49].

Poor appetite and weight loss are common symptoms of geriatric depression, in which the resulting poor mobility and balance may also increase the risk of falls. Shahar et al. (2009) reported that nutritional deficiencies in vitamin D and folate were related to falls in older adults living in senior living facilities [50]. A recent systematic review found some evidence for the association between vitamin D insufficiency and depression [51], but it is unknown whether low vitamin D levels are a cause, consequence or indirect correlate of depression [52].

Depression is associated with a characteristic pattern of cognitive deficits affecting mainly episodic memory, processing speed and executive function including attention and cognitive flexibility [53]. Cognitive decline due to major depression has been named “pseudodementia” [8]. When a major depressive episode is successfully treated, memory problems often fully abate. However, in older persons, a major depressive episode may sometimes be an expression of an irreversible dementia syndrome [8]. As discussed in early chapters of this book, cognitive domains especially related to gait regulation are attention and executive function [54] which are needed to allocate greater attention while walking to compensate for age-associated declines in sensory and motor function. When walking with distractions, depressive symptoms and deficits in executive function are associated with increased unsteadiness [55]. Deficits in executive function associated with depression may also increase the risk of falls, as we describe in the following section of this chapter on “[Cognition and Falls](#)” [56].

Although other symptoms of depression including psychomotor retardation, anergia, anhedonia and abulia may also complexly contribute to falls, it is still unclear. Future studies will be needed to examine the influence of each symptom on the incidence of falls.

## Antidepressants and Falls

Although antidepressant medication can mitigate depressive symptoms, which should lower fall risks, it also increases fall risk independent from depression. Among 488 older adults in the community, although most people who were using antidepressant medication did no longer experience depressive symptoms (with only 18% scoring  $\geq 5$  on GDS-15), the use of antidepressants was an independent risk factor for falls [57]. A systematic review and meta-analysis found that the use of antidepressants increased the risk of falls by 68% [58]. For more details, please refer to Chap. 9.

## Fear of Falling and Falls

Fear of falling (FoF) is a major mental health problem in community-dwelling older adults characterized both by the loss of self-confidence/self-efficacy in their balance abilities and by activity avoidance related to an excessive concern of falling. Physical, psychological and social changes caused by FoF were observed in older adults [59–62], indicating that FoF is considered both a cause and a consequence of adverse health outcomes.

### Prevalence and Risk Factors of FoF

The prevalence of FoF among older adults living in the community varies between 21% and 85% [63]. For older adults who experienced falls, FoF is reported in 29–92% [61, 64]. The variability in the prevalence of FoF is likely due to the various definitions and instruments used to measure FoF. It has been suggested that when a dichotomous response is required to answer the question “are you afraid of falling?”, a lower prevalence may be evident [65]; in contrast, when a response requires to indicate the degree of fear (e.g. how much are you afraid of falling), an increased prevalence may be evident [59, 61]. Despite the variation of the prevalence, it is clear that FoF is a significant psychological issue in older adults.

FoF is more prevalent among women than men [62, 63]. While this is reasonable because women are predisposed to mobility limitations and frailty [66], some studies caution that FoF in men may be underreported due to the perceived stigma associated with the reporting of their fears [67, 68].

The incidence of newly developed FoF is about 20% among community-dwelling older adults over a 2-year period [69, 70] although it may vary depending on individual’s characteristics (e.g. age and physical condition). In this regard, it has been indicated that experience of at least one fall [71–73], increased age [61, 63, 65], female sex [62, 63], dizziness [61, 72] and decline in physical functioning, particularly gait and balance dysfunction [63, 65, 69, 74], are risk factors associated with FoF. Furthermore, some studies have suggested that FoF may actually be a manifestation of generalized anxiety, depressive mood and neuroticism similarly to other fears that plague older adults [75, 76]. Therefore, it is considered that FoF is characterized by multifactorial etiology and the interaction between physical and psychological deficits may be involved in the onset of new FoF.

### Assessment Tools for FoF

The simplest assessment is a single and dichotomized question in which the participant is required to respond either “yes/no” or “fear/no fear” to the question: “Are you afraid of falling?” Although this question has the advantage of being straightforward and easy to generate prevalence estimates, it was later criticized due to its limited ability to measure the different levels of FoF in various circumstances.

The Falls Efficacy Scale (FES), developed by Tinetti et al. in 1990, includes ten question items that assess the degree of perceived self-efficacy in avoiding a fall during basic activities of daily life such as house cleaning, getting dressed and simple shopping [74]. Low self-efficacy is used interchangeably with FoF. Because it measures only simple indoor activities, the FES is most suitable for older adults who are homebound and have low mobility but not for physically active/high-functioning older adults.

The Activities-Specific Balance Confidence Scale (ABC), developed by Powell and Myers in 1995, includes 16 question items and asks participants to rate their balance confidence on a visual analog scale (0–100) [77]. The ABC assesses individual's confidence and ability to perform activities outside their home, such as walking in a crowded mall or riding an escalator holding onto the railing that are of greater difficulty than the ones measured using FES. The ABC is therefore suitable for older adults with high physical activity.

The Survey of Activities and Fear of Falling in the Elderly (SAFFE), developed by Lachman et al. in 1998, assesses the effects of FoF on factors such as activity restriction or poor quality of life [78]. This survey examines 11 activities of daily life, including instrumental activities of daily living, mobility tasks and social activities (e.g. taking a shower, going to the store, taking public transportation and going to the movies or shows). The most distinctive feature of the SAFFE is that it includes social activities in the assessment, because avoidance of these activities may signal early-onset FoF.

## The Association of FoF with the Risk of Falls

In early studies, FoF was defined as a “post-fall syndrome”; therefore, by definition, a fall consists a strong risk factor for the development of FoF. Surprisingly, FoF was present both in older adults who have fallen and in those who have not experienced a fall [62, 63, 65, 79], suggesting that FoF formed a reciprocal causal association with the incidence of falls. In a large prospective study, Friedman et al. (2002) demonstrated that FoF at baseline was an independent predictor of incidental falls. Furthermore, previous falls at baseline also predicted new development of FoF [80].

Although reduced physical ability (e.g. slower gait speed and poor balance) may mostly cause FoF and falls, FoF-related avoidance of activities can also mediate the link between FoF and increased risk of falls (Fig. 4.2). Previous studies confirmed that FoF lead to an increase in restricting or avoiding activities [60, 65, 73]. This FoF-related activity restriction may have negative long-term effects on physical abilities, which increases the risk of falls because it leads to muscle atrophy, deconditioning and poor balance. Indeed, a previous study that targeted well-functioning adults 65–70 years old showed that FoF with activity restriction, but not FoF without activity restriction, was independently associated with decreased stride velocity and stride length, increased gait variability and total double support and reduced step cadence [81]. However, since no studies have concluded that FoF is a risk factor for falls, independent of impaired physical functioning (e.g. balance and gait function), cautious interpretation is advisable.



deficits in efficiently planning the motor execution to elude falling. More recently, in a study measuring motor imagery ability (the ability to accurately imagine an action without actual execution), Sakurai et al. (2017) demonstrated that older adults with FoF showed higher incongruence between imagined actions and actual actions (i.e. overestimation of their gait performance), reflecting impaired motor planning [93]. Unfortunately, these cross-sectional studies preclude us from drawing inferences about the potential causal relationships between FoF-related motor planning deficits and falling. However, the association between the deficit in motor planning and FoF is supported by a functional imaging study showing that hypometabolism (i.e. reduced neural activity) in the supplementary motor area (BA6), which is involved in motor planning and motor coordination, contributed to the development of FoF [70].

---

## Cognition and Falls

The motor and sensory systems are linked by higher-order neurological processes and cognition, which are required for planning movements, divided attention and responding to changes within the environment [94, 95]. Indeed, recent studies have demonstrated that cognition is key in the regulation of gait and balance in older adults [94, 96], and thus cognitive impairment is suggested to be related to an increased risk of fall.

### Global Cognition

Dementia and falls often co-exist in older adults; the fall rate in older adults with dementia was reported to be up to eight times higher than in older adults without dementia [97–101]. A longitudinal study showed that the annual incidence of falls was up to 85% in older adults with dementia [102]. The consequences of falls in the population of demented older adults are very serious; when compared to older adults without dementia, older adults with dementia were approximately three times more likely to sustain a hip fracture [103, 104]. They were also less likely to make a good functional recovery after significant injury than the cognitively intact older adults [104].

The significant association between increased fall risk and cognitive impairment also applies to older adults without diagnosed dementia. A previous study showed that, in community-dwelling older adults, older adults with cognitive impairment determined with the short portable mental status questionnaire were five times more likely to fall than cognitively intact older adults [99]. This study also indicated that the influence of cognitive impairment on the risk of fall exceeded the impaired functioning-related risk factors for fall, such as lower extremity dysfunction and impaired balance and gait [99]. The Mini-Mental State Exam (MMSE) was the most commonly used measurement of global cognition. Previous studies showed that low MMSE scores have also been associated with an increased fall risk in older

adults [105, 106]. Ramirez et al. (2010) examined the predictive ability of the MMSE domains (orientation to time, orientation to place, registration, attention and calculation, recall, language and visual construction) for falls. The results showed that older adults with impaired place orientation and visual construction were most likely to fall [106]. However, meta-analysis conducted by Muir et al. (2012) indicated that measurements of global cognitive status were not consistently associated with falls (only one third of the studies showed a significant association); however, the MMSE was strongly associated with serious fall-related injury in community-dwelling older adults [107]. These results suggested that although impaired global cognition was associated with the inability of avoidance behaviour (e.g. stepping action and successful defensive position) when individuals fall, the risk of fall may be increased in case of impairment of other cognitive domains.

## Executive Function (EF)

Safe and independent mobility function requires well-coordinated gait while generating several sensory inputs. This process has long been considered to be automated and controlled primarily by reflex activity. However, emerging evidence suggests that gait is no longer considered a merely automated motor activity but rather an activity that requires cognition, such as executive function (EF). The seminal “stops walking while talking” study by Lundin-Olsson et al. (1997) showed that the inability to maintain a conversation while walking was an indication of future falls in older nursing home residents [108]. If the locomotion was automatic, the performance of attention-demanding dual tasks during walking would not alter the gait pattern. This prompted extensive investigation of lower dual-task gait performance (declines in gait performance during simultaneous performance of a secondary cognitive task) that demonstrated an interesting relationship between the regulation of the locomotor and EF, as potential contributors to fall risk in older adults.

Although there is no generally accepted definition of EF, there is consensus that EF consists of cognitive processes of attention, working memory, task flexibility and inhibition [109]. Impairment of EF had a significant impact on postural control and gait and thus increases fall risk. Notably, impairment of EF was observed in healthy and well-functioning people without impaired global cognitive status [42]. A decline in EF was associated with an increased risk of falls not only in older adults with Alzheimer’s disease [110] but also in older adults without overt cognitive impairment [42]. These results suggest that cognitive risk factors for falls in people with dementia (i.e. impairment of EF) may evolve prior to clinically evident dementia.

Trail-Making Test A (TMT-A) assesses visual search, motor speed skills and attention, while TMT-B assesses working memory and task-shifting (e.g. cognitive flexibility). These tests were frequently used as a stand-alone measurement of EF and showed the association of EF with the risk of falls [111]. Nevitt et al. (1991) showed that slower performance on TMT-B (>180 s) was independently associated with a major injury from a fall [112]. Furthermore, Pijnappels et al. (2010) found



significantly poorer performance on TMT-B in people that fall recurrently compared to people who do not fall [113]. A previous study using the difference between TMT-B minus TMT-A ( $\Delta$ TMT), which is considered as a highly representative measurement of EF (i.e. cognitive flexibility, working memory, and divided attention), showed that there was increased likelihood of falling for people with poorer performance on  $\Delta$ TMT; in addition, increased  $\Delta$ TMT score ( $>50$  s) was the next discriminating factor for the risk of injurious or recurrent falls [114]. These results were supported by findings from a previous neuroimaging study that gait control (e.g. gait velocity) and EF detected by TMT may share the same neural substrate, such as the primary sensorimotor cortex [115].

Low performance on Digit Symbol scores, which indicates impaired processing speed, has been associated with an increased risk of injurious falls [116, 117]. For instance, a large cohort study of 5356 participants by Welmerink et al. (2010) demonstrated that older adults with slightly decreased Digit Symbol Substitution Test scores were at increased risk of a serious fall, which was defined as a fall causing an injury requiring hospital admission [117]. Poor ability of choice reaction time, which is a measure of processing speed, has also shown good discrimination function between people who fall and those who do not [35]. In addition to processing speed, a recent study indicated the increased risk of falls in older adults with poor inhibition. Schoene et al. (2017) used choice stepping reaction time task (CSRT, requiring rapid decision making and step initiation) and inhibitory CSRT (iCSRT, requiring additional response inhibition and response selection, such as go/no-go task) to show that a measure of inhibition (i.e. iCSRT-CSRT) was predictive for falls [118].

Assessing the dual-task gait paradigm (walking while performing a cognitive challenge) elucidates the interaction between cognition, motor and the risk of falls. The magnitude of these decrements in the performance of dual tasking (dual-task costs) reveals the insufficiency of the cortical control to regulate walking and has been associated with an increased fall risk. The underlying reasons that reduce the dual-tasking ability, related to future incidence of fall, have not been fully elucidated. A possible explanation is that older adults who fall frequently have an inherently reduced attentional capacity, which demands them greater attentional resources due to their impaired postural control and gait system (i.e. attentional limitations model). Another possible reason for the association is that older people who fall have difficulty in allocating attention between two tasks. The close association between the ability to perform dual-task gait and falls is comprehensively described in Chap. 6.

## Self-Awareness for Physical Ability

High consistency between how well individuals can actually perform a task and how well they think they can perform this task increases the chance of successful goal-directed behaviour. Therefore, correct estimation of one's physical abilities is essential to safely perform daily activities. This is accentuated in older adults as physical abilities deteriorate with age. As a result, individuals unaware of their

impairments may engage in unsafe and excessively challenging tasks, putting themselves at risk (e.g. tripping and stumbling while walking). However, older adults, particularly demented people, often overestimate their physical ability. van Iersel et al. (2006) demonstrated that gait velocity in older adults with dementia was disproportionately fast when adjusted for their overall degree of physical impairment [119]. Unawareness of reduced physical ability, such as reaching abilities and stepping over, was observed in non-demented older adults [120–123] and was associated with past and future falls [124, 125]. Robinovitch and Cronin (1999) provided evidence that older adults tended to overestimate their reaching ability, whereas young adults tended to underestimate it [120]. Furthermore, Sakurai et al. (2013) previously showed that older adults tended to overestimate their step-over ability, and the number of older adults who fall, who overestimated their step-over ability, was almost double than those who do not fall [125]. A recent longitudinal study indeed showed that overestimation of step-out ability highly predicted future falls over a period of 1 year (relative risk was 18.8) [124]. Overestimation of physical capabilities can be an additional explanation of the high risk of falls observed in both demented and non-demented older adults. The failure to observe one's own functional decline has been influenced by neural changes in the anterior prefrontal cortex, particularly in the orbitofrontal cortex which is involved in adequate self-appraisals [126–128].

---

## Conclusion

There is considerable evidence that depression, FoF, and deficits in executive function are associated with falls among older adults. Although these risk factors, particularly FoF, do not always directly contribute to incidence of falls, we cannot deny that assessing these factors is useful for detecting the risk of older adults' falling at an earlier stage. Because the factors contributing to falls are interrelated and affect important health outcomes such as symptom burden and functional loss, comprehensive fall risk assessments and prevention strategies are needed to provide appropriate and prompt treatments, which will result in multiple health benefits.

---

## References

1. Mutran EJ, Reitzes DC, Mossey J, Fernandez ME. Social support, depression, and recovery of walking ability following hip fracture surgery. *J Gerontol B Psychol Sci Soc Sci*. 1995;50(6):S354–61.
2. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS. Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1999;159(5):484–90.
3. Miller RR, Ballew SH, Shardell MD, Hicks GE, Hawkes WG, Resnick B, et al. Repeat falls and the recovery of social participation in the year post-hip fracture. *Age Ageing*. 2009;38(5):570–5.

4. Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci*. 2003;58(3):249–65.
5. Weinberger AH, Gbedemah M, Martinez AM, Nash D, Galea S, Goodwin RD. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. *Psychol Med*. 2018;48(8):1308–15.
6. Beekman AT, Deeg DJ, van Tilburg T, Smit JH, Hooijer C, van Tilburg W. Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord*. 1995;36(1–2):65–75.
7. Fiske A, Wetherell JL, Gatz M. Depression in older adults. *Annu Rev Clin Psychol*. 2009;5:363–89.
8. American Psychological Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychological Association; 1994.
9. Nease DE Jr, Maloin JM. Depression screening: a practical strategy. *J Fam Pract*. 2003;52(2):118–24.
10. Williams JW Jr, Noel PH, Cordes JA, Ramirez G, Pignone M. Is this patient clinically depressed? *JAMA*. 2002;287(9):1160–70.
11. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385–401.
12. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*. 1997;12(2):277–87.
13. Brink TL, Yesavage JA, Lum O, Heersema PH, Adey M, Rose TL. Screening tests for geriatric depression. *Clin Gerontol*. 1982;1(1):37–43.
14. D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. *Fam Pract*. 1994;11(3):260–6.
15. Burke WJ, Roccaforte WH, Wengel SP. The short form of the Geriatric Depression Scale: a comparison with the 30-item form. *J Geriatr Psychiatry Neurol*. 1991;4(3):173–8.
16. Kemp BJ, Adams BM, Campbell ML. Depression and life satisfaction in aging polio survivors versus age-matched controls: relation to postpolio syndrome, family functioning, and attitude toward disability. *Arch Phys Med Rehabil*. 1997;78(2):187–92.
17. Kemp BJ, Krause JS. Depression and life satisfaction among people ageing with post-polio and spinal cord injury. *Disabil Rehabil*. 1999;21(5–6):241–9.
18. Spitzer RL, Williams JB, Kroenke K, Linzer M, deGruy FV 3rd, Hahn SR, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. *JAMA*. 1994;272(22):1749–56.
19. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient health questionnaire. *JAMA*. 1999;282(18):1737–44.
20. Quach L, Yang FM, Berry SD, Newton E, Jones RN, Burr JA, et al. Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. *J Gerontol A Biol Sci Med Sci*. 2013;68(12):1575–81.
21. Stalenhoef PA, Diederiks JP, Knottnerus JA, Kester AD, Crebolder HF. A risk model for the prediction of recurrent falls in community-dwelling elderly: a prospective cohort study. *J Clin Epidemiol*. 2002;55(11):1088–94.
22. Wei TS, Liu PT, Chang LW, Liu SY. Gait asymmetry, ankle spasticity, and depression as independent predictors of falls in ambulatory stroke patients. *PLoS One*. 2017;12(5):e0177136.
23. Menant JC, Wong AK, Trollor JN, Close JC, Lord SR. Depressive symptoms and orthostatic hypotension are risk factors for unexplained falls in community-living older people. *J Am Geriatr Soc*. 2016;64(5):1073–8.
24. Kron M, Loy S, Sturm E, Nikolaus T, Becker C. Risk indicators for falls in institutionalized frail elderly. *Am J Epidemiol*. 2003;158(7):645–53.

25. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology*. 2010;21(5):658–68.
26. Jung S, Lee S, Lee S, Bae S, Imaoka M, Harada K, et al. Relationship between physical activity levels and depressive symptoms in community-dwelling older Japanese adults. *Geriatr Gerontol Int*. 2018;18(3):421–7.
27. Lee DA, Lalor AF, Russell G, Stolwyk R, Brown T, McDermott F, et al. Understanding temporal relationships between depression, falls, and physical activity in a cohort of post-hospitalized older adults – a breakthrough or a conundrum? *Int Psychogeriatr*. 2017;29(10):1681–92.
28. Bauer LK, Caro MA, Beach SR, Mastromauro CA, Lenihan E, Januzzi JL, et al. Effects of depression and anxiety improvement on adherence to medication and health behaviors in recently hospitalized cardiac patients. *Am J Cardiol*. 2012;109(9):1266–71.
29. Berry SD, Quach L, Procter-Gray E, Kiel DP, Li W, Samelson EJ, et al. Poor adherence to medications may be associated with falls. *J Gerontol A Biol Sci Med Sci*. 2010;65(5):553–8.
30. Michalak J, Troje NF, Fischer J, Vollmar P, Heidenreich T, Schulte D. Embodiment of sadness and depression--gait patterns associated with dysphoric mood. *Psychosom Med*. 2009;71(5):580–7.
31. Hausdorff JM, Peng CK, Goldberger AL, Stoll AL. Gait unsteadiness and fall risk in two affective disorders: a preliminary study. *BMC Psychiatry*. 2004;4:39.
32. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil*. 2001;82(8):1050–6.
33. Maki BE. Gait changes in older adults: predictors of falls or indicators of fear. *J Am Geriatr Soc*. 1997;45(3):313–20.
34. Kvelde T, Pijnappels M, Delbaere K, Close JC, Lord SR. Physiological and cognitive mediators for the association between self-reported depressed mood and impaired choice stepping reaction time in older people. *J Gerontol A Biol Sci Med Sci*. 2010;65(5):538–44.
35. Lord SR, Fitzpatrick RC. Choice stepping reaction time: a composite measure of falls risk in older people. *J Gerontol A Biol Sci Med Sci*. 2001;56(10):M627–32.
36. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med*. 2008;358(1):55–68.
37. Hasler G. Pathophysiology of depression: do we have any solid evidence of interest to clinicians? *World Psychiatry*. 2010;9(3):155–61.
38. Douglas KM, Porter RJ, Knight RG, Maruff P. Neuropsychological changes and treatment response in severe depression. *Br J Psychiatry*. 2011;198(2):115–22.
39. Douglas KM, Porter RJ. Longitudinal assessment of neuropsychological function in major depression. *Aust N Z J Psychiatry*. 2009;43(12):1105–17.
40. Koolschijn PC, van Haren NE, Lensvelt-Mulders GJ, Hulshoff Pol HE, Kahn RS. Brain volume abnormalities in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Hum Brain Mapp*. 2009;30(11):3719–35.
41. Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res*. 2002;53(2):647–54.
42. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci*. 2010;65(10):1086–92.
43. Zheng JJ, Lord SR, Close JC, Sachdev PS, Wen W, Brodaty H, et al. Brain white matter hyperintensities, executive dysfunction, instability, and falls in older people: a prospective cohort study. *J Gerontol A Biol Sci Med Sci*. 2012;67(10):1085–91.
44. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963–74.
45. Sneed JR, Culang-Reinlieb ME. The vascular depression hypothesis: an update. *Am J Geriatr Psychiatry*. 2011;19(2):99–103.
46. Hajjar I, Yang F, Sorond F, Jones RN, Milberg W, Cupples LA, et al. A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: relationship to blood pressure and other cardiovascular risks. *J Gerontol A Biol Sci Med Sci*. 2009;64(9):994–1001.

47. Hajjar I, Quach L, Yang F, Chaves PH, Newman AB, Mukamal K, et al. Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. *Circulation*. 2011;123(8):858–65.
48. Stone KL, Ancoli-Israel S, Blackwell T, Ensrud KE, Cauley JA, Redline S, et al. Actigraphy-measured sleep characteristics and risk of falls in older women. *Arch Intern Med*. 2008;168(16):1768–75.
49. Stone KL, Blackwell TL, Ancoli-Israel S, Cauley JA, Redline S, Marshall LM, et al. Sleep disturbances and risk of falls in older community-dwelling men: the outcomes of Sleep Disorders in Older Men (MrOS Sleep) Study. *J Am Geriatr Soc*. 2014;62(2):299–305.
50. Shahar D, Levi M, Kurtz I, Shany S, Zvili I, Mualleme E, et al. Nutritional status in relation to balance and falls in the elderly: a preliminary look at serum folate. *Ann Nutr Metab*. 2009;54(1):59–66.
51. Parker GB, Brotchie H, Graham RK. Vitamin D and depression. *J Affect Disord*. 2017;208:56–61.
52. Parker G, Brotchie H. “D” for depression: any role for vitamin D? “Food for thought” II Parker and Brotchie vitamin D and depression. *Acta Psychiatr Scand*. 2011;124(4):243–9.
53. McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. *J Affect Disord*. 2009;119(1–3):1–8.
54. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329–42; quiz 472.
55. Hausdorff JM, Schweiger A, Herman T, Yogev-Seligmann G, Giladi N. Dual-task decrements in gait: contributing factors among healthy older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63(12):1335–43.
56. Holtzer R, Friedman R, Lipton RB, Katz M, Xue X, Verghese J. The relationship between specific cognitive functions and falls in aging. *Neuropsychology*. 2007;21(5):540–8.
57. Kvelde T, Lord SR, Close JC, Reppermund S, Kochan NA, Sachdev P, et al. Depressive symptoms increase fall risk in older people, independent of antidepressant use, and reduced executive and physical functioning. *Arch Gerontol Geriatr*. 2015;60(1):190–5.
58. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med*. 2009;169(21):1952–60.
59. Cumming RG, Salkeld G, Thomas M, Szonyi G. Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores, and nursing home admission. *J Gerontol A Biol Sci Med Sci*. 2000;55(5):M299–305.
60. Delbaere K, Crombez G, Vanderstraeten G, Willems T, Cambier D. Fear-related avoidance of activities, falls and physical frailty. A prospective community-based cohort study. *Age Ageing*. 2004;33(4):368–73.
61. Howland J, Peterson EW, Levin WC, Fried L, Pordon D, Bak S. Fear of falling among the community-dwelling elderly. *J Aging Health*. 1993;5(2):229–43.
62. Legters K. Fear of falling. *Phys Ther*. 2002;82(3):264–72.
63. Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE. Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing*. 2008;37(1):19–24.
64. Aoyagi K, Ross PD, Davis JW, Wasnich RD, Hayashi T, Takemoto T. Falls among community-dwelling elderly in Japan. *J Bone Miner Res*. 1998;13(9):1468–74.
65. Arfken CL, Lach HW, Birge SJ, Miller JP. The prevalence and correlates of fear of falling in elderly persons living in the community. *Am J Public Health*. 1994;84(4):565–70.
66. Shamliyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. *Ageing Res Rev*. 2013;12(2):719–36.
67. Maki BE, Holliday PJ, Topper AK. Fear of falling and postural performance in the elderly. *J Gerontol*. 1991;46(4):M123–31.
68. McAuley E, Mihalko SL, Rosengren K. Self-efficacy and balance correlates of fear of falling in the elderly. *J Aging Phys Act*. 1997;5(4):329–40.

69. Lach HW. Incidence and risk factors for developing fear of falling in older adults. *Public Health Nurs.* 2005;22(1):45–52.
70. Sakurai R, Fujiwara Y, Yasunaga M, Suzuki H, Kanosue K, Montero-Odasso M, et al. Association between hypometabolism in the supplementary motor area and fear of falling in older adults. *Front Aging Neurosci.* 2017;9:251.
71. Chu CL, Liang CK, Chow PC, Lin YT, Tang KY, Chou MY, et al. Fear of falling (FF): psychosocial and physical factors among institutionalized older Chinese men in Taiwan. *Arch Gerontol Geriatr.* 2011;53(2):e232–6.
72. Murphy SL, Dubin JA, Gill TM. The development of fear of falling among community-living older women: predisposing factors and subsequent fall events. *J Gerontol A Biol Sci Med Sci.* 2003;58(10):M943–7.
73. Murphy SL, Williams CS, Gill TM. Characteristics associated with fear of falling and activity restriction in community-living older persons. *J Am Geriatr Soc.* 2002;50(3):516–20.
74. Tinetti ME, Richman D, Powell L. Falls efficacy as a measure of fear of falling. *J Gerontol.* 1990;45(6):P239–43.
75. Delbaere K, Close JC, Brodaty H, Sachdev P, Lord SR. Determinants of disparities between perceived and physiological risk of falling among elderly people: cohort study. *BMJ.* 2010;341:c4165.
76. Mann R, Birks Y, Hall J, Torgerson D, Watt I. Exploring the relationship between fear of falling and neuroticism: a cross-sectional study in community-dwelling women over 70. *Age Ageing.* 2006;35(2):143–7.
77. Powell LE, Myers AM. The activities-specific balance confidence (ABC) scale. *J Gerontol A Biol Sci Med Sci.* 1995;50A(1):M28–34.
78. Lachman ME, Howland J, Tennstedt S, Jette A, Assmann S, Peterson EW. Fear of falling and activity restriction: the survey of activities and fear of falling in the elderly (SAFE). *J Gerontol B Psychol Sci Soc Sci.* 1998;53(1):P43–50.
79. Jorstad EC, Hauer K, Becker C, Lamb SE. Measuring the psychological outcomes of falling: a systematic review. *J Am Geriatr Soc.* 2005;53(3):501–10.
80. Friedman SM, Munoz B, West SK, Rubin GS, Fried LP. Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. *J Am Geriatr Soc.* 2002;50(8):1329–35.
81. Rochat S, Bula CJ, Martin E, Seematter-Bagnoud L, Karmaniola A, Aminian K, et al. What is the relationship between fear of falling and gait in well-functioning older persons aged 65 to 70 years? *Arch Phys Med Rehabil.* 2010;91(6):879–84.
82. Ayoubi F, Launay C, Annweiler C, Fantino B, Kabeshova A, Beauchet O. Fear of falling, falls, and gait variability in older community-dwelling individuals: is there an association? *J Am Geriatr Soc.* 2013;61(7):1236–8.
83. Herman T, Giladi N, Gurevich T, Hausdorff JM. Gait instability and fractal dynamics of older adults with a “cautious” gait: why do certain older adults walk fearfully? *Gait Posture.* 2005;21(2):178–85.
84. Asai T, Misu S, Doi T, Yamada M, Ando H. Effects of dual-tasking on control of trunk movement during gait: respective effect of manual- and cognitive-task. *Gait Posture.* 2014;39(1):54–9.
85. Sawa R, Doi T, Misu S, Tsutsumimoto K, Nakakubo S, Asai T, et al. The association between fear of falling and gait variability in both leg and trunk movements. *Gait Posture.* 2014;40(1):123–7.
86. Hausdorff JM. Gait variability: methods, modeling and meaning. *J Neuroeng Rehabil.* 2005;2:19.
87. Verghese J, Holtzer R, Lipton RB, Wang C. Quantitative gait markers and incident fall risk in older adults. *J Gerontol A Biol Sci Med Sci.* 2009;64(8):896–901.
88. Verghese J, Ambrose AF, Lipton RB, Wang C. Neurological gait abnormalities and risk of falls in older adults. *J Neurol.* 2010;257(3):392–8.
89. Ayoubi F, Launay CP, Annweiler C, Beauchet O. Fear of falling and gait variability in older adults: a systematic review and meta-analysis. *J Am Med Dir Assoc.* 2015;16(1):14–9.



90. Uemura K, Yamada M, Nagai K, Ichihashi N. Older adults at high risk of falling need more time for anticipatory postural adjustment in the precrossing phase of obstacle negotiation. *J Gerontol A Biol Sci Med Sci*. 2011;66(8):904–9.
91. Uemura K, Yamada M, Nagai K, Tanaka B, Mori S, Ichihashi N. Fear of falling is associated with prolonged anticipatory postural adjustment during gait initiation under dual-task conditions in older adults. *Gait Posture*. 2012;35(2):282–6.
92. Young WR, Mark WA. How fear of falling can increase fall-risk in older adults: applying psychological theory to practical observations. *Gait Posture*. 2015;41(1):7–12.
93. Sakurai R, Fujiwara Y, Yasunaga M, Suzuki H, Sakuma N, Imanaka K, et al. Older adults with fear of falling show deficits in motor imagery of gait. *J Nutr Health Aging*. 2017;21(6):721–6.
94. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60(11):2127–36.
95. Clark DJ. Automaticity of walking: functional significance, mechanisms, measurement and rehabilitation strategies. *Front Hum Neurosci*. 2015;9:246.
96. Montero-Odasso M, Oteng-Amoako A, Speechley M, Gopaul K, Beauchet O, Annweiler C, et al. The motor signature of mild cognitive impairment: results from the gait and brain study. *J Gerontol A Biol Sci Med Sci*. 2014;69(11):1415–21.
97. Guo Z, Wills P, Viitanen M, Fastbom J, Winblad B. Cognitive impairment, drug use, and the risk of hip fracture in persons over 75 years old: a community-based prospective study. *Am J Epidemiol*. 1998;148(9):887–92.
98. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. *PLoS One*. 2009;4(5):e5521.
99. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319(26):1701–7.
100. Horikawa E, Matsui T, Arai H, Seki T, Iwasaki K, Sasaki H. Risk of falls in Alzheimer's disease: a prospective study. *Intern Med*. 2005;44(7):717–21.
101. van Doorn C, Gruber-Baldini AL, Zimmerman S, Hebel JR, Port CL, Baumgarten M, et al. Dementia as a risk factor for falls and fall injuries among nursing home residents. *J Am Geriatr Soc*. 2003;51(9):1213–8.
102. Shaw FE. Falls in cognitive impairment and dementia. *Clin Geriatr Med*. 2002;18(2):159–73.
103. Melton LJ 3rd, Beard CM, Kokmen E, Atkinson EJ, O'Fallon WM. Fracture risk in patients with Alzheimer's disease. *J Am Geriatr Soc*. 1994;42(6):614–9.
104. Friedman SM, Menzies IB, Bukata SV, Mendelson DA, Kates SL. Dementia and hip fractures: development of a pathogenic framework for understanding and studying risk. *Geriatr Orthop Surg Rehabil*. 2010;1(2):52–62.
105. van Schoor NM, Smit JH, Pluijm SM, Jonker C, Lips P. Different cognitive functions in relation to falls among older persons. Immediate memory as an independent risk factor for falls. *J Clin Epidemiol*. 2002;55(9):855–62.
106. Ramirez D, Wood RC, Becho J, Owings K, Markides K, Espino DV. Mini-mental state exam domains predict falls in an elderly population: follow-up from the Hispanic Established Populations for Epidemiologic Studies of the Elderly (H-EPESE) study. *Ethn Dis*. 2010;20(1):48–52.
107. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299–308.
108. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. *Lancet*. 1997;349(9052):617.
109. Suchy Y. Executive functioning: overview, assessment, and research issues for non-neuropsychologists. *Ann Behav Med*. 2009;37(2):106–16.
110. Sheridan PL, Hausdorff JM. The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2007;24(2):125–37.

111. Kearney FC, Harwood RH, Gladman JR, Lincoln N, Masud T. The relationship between executive function and falls and gait abnormalities in older adults: a systematic review. *Dement Geriatr Cogn Disord*. 2013;36(1–2):20–35.
112. Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. *J Gerontol*. 1991;46(5):M164–70.
113. Pijnappels M, Delbaere K, Stumieks DL, Lord SR. The association between choice stepping reaction time and falls in older adults—a path analysis model. *Age Ageing*. 2010;39(1):99–104.
114. Delbaere K, Close JC, Heim J, Sachdev PS, Brodaty H, Slavin MJ, et al. A multifactorial approach to understanding fall risk in older people. *J Am Geriatr Soc*. 2010;58(9):1679–85.
115. Sakurai R, Ishii K, Yasunaga M, Takeuchi R, Murayama Y, Sakuma N, et al. The neural substrate of gait and executive function relationship in elderly women: a PET study. *Geriatr Gerontol Int*. 2017;17(11):1873–80.
116. Anstey KJ, von Sanden C, Luszcz MA. An 8-year prospective study of the relationship between cognitive performance and falling in very old adults. *J Am Geriatr Soc*. 2006;54(8):1169–76.
117. Welmerink DB, Longstreth WT Jr, Lyles MF, Fitzpatrick AL. Cognition and the risk of hospitalization for serious falls in the elderly: results from the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci*. 2010;65(11):1242–9.
118. Schoene D, Delbaere K, Lord SR. Impaired response selection during stepping predicts falls in older people—a cohort study. *J Am Med Dir Assoc*. 2017;18(8):719–25.
119. van Iersel MB, Verbeek AL, Bloem BR, Munneke M, Esselink RA, Rikkert MG. Frail elderly patients with dementia go too fast. *J Neurol Neurosurg Psychiatry*. 2006;77(7):874–6.
120. Robinovitch SN, Cronin T. Perception of postural limits in elderly nursing home and day care participants. *J Gerontol A Biol Sci Med Sci*. 1999;54(3):B124–30; discussion B31.
121. Sakurai R, Fujiwara Y, Sakuma N, Suzuki H, Ishihara M, Higuchi T, et al. Influential factors affecting age-related self-overestimation of step-over ability: focusing on frequency of going outdoors and executive function. *Arch Gerontol Geriatr*. 2014;59(3):577–83.
122. Liu-Ambrose T, Ahamed Y, Graf P, Feldman F, Robinovitch SN. Older fallers with poor working memory overestimate their postural limits. *Arch Phys Med Rehabil*. 2008;89(7):1335–40.
123. Sakurai R, Fujiwara Y, Ishihara M, Yasunaga M, Ogawa S, Suzuki H, et al. Self-estimation of physical ability in stepping over an obstacle is not mediated by visual height perception: a comparison between young and older adults. *Psychol Res*. 2017;81(4):740–9.
124. Fujimoto A, Hori H, Tamura T, Hirai T, Umemura T, Iguchi F, et al. Relationships between estimation errors and falls in healthy aged dwellers. *Gerontology*. 2015;61(2):109–15.
125. Sakurai R, Fujiwara Y, Ishihara M, Higuchi T, Uchida H, Imanaka K. Age-related self-overestimation of step-over ability in healthy older adults and its relationship to fall risk. *BMC Geriatr*. 2013;13:44.
126. Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science*. 2004;306(5695):443–7.
127. Shany-Uri T, Lin N, Rosen HJ, Sollberger M, Miller BL, Rankin KP. Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention. *Brain J Neurol*. 2014;137(Pt 8):2368–81.
128. Sakurai R, Fujiwara Y, Yasunaga M, Suzuki H, Murayama Y, Imanaka K, et al. Neural correlates of older adults' self-overestimation of stepping-over ability. *Age*. 2016;38(4):351–61.





# Frailty, Cognition, and Falls

# 5

Lindsay M. K. Wallace, Olga Theou,  
and Kenneth Rockwood

## Frailty

### What Is Frailty and Why Is It Important?

Frailty in a statistical sense is understood as variability in the risk of adverse outcomes in people with the same degree of exposure. This reflects it being originally employed as a way to understand variability in the risk of death of people of the same age. Clinically, frailty can be understood as vulnerability to poor health outcomes due to decreased physiologic reserve. There is still much heterogeneity in health status and mortality risk among people of the same age; in other words, frailty is associated with, but independent of, chronological age. Using frailty to explain some of these individual differences may be useful to better understand “biological ageing” and improve risk prediction and care management in older adults.

The decline in physiologic reserve that characterizes frailty produces conditions where even minor insults can give rise to catastrophic results such as falls, delirium, disability, hospitalization, institutionalization, and mortality. Measuring frailty can assist clinicians in understanding how to best manage patients. This means balancing between withholding treatments that are likely to harm – based either on the

---

L. M. K. Wallace

Faculty of Graduate Studies, Dalhousie University, Halifax, NS, Canada

Geriatric Medicine Research Unit, Centre for Health Care of the Elderly, Nova Scotia Health Authority, Halifax, NS, Canada

e-mail: [Lindsay.Wallace@dal.ca](mailto:Lindsay.Wallace@dal.ca)

O. Theou · K. Rockwood (✉)

Geriatric Medicine Research Unit, Centre for Health Care of the Elderly, Nova Scotia Health Authority, Halifax, NS, Canada

Department of Medicine, Dalhousie University, Halifax, NS, Canada

e-mail: [Olga.Theou@dal.ca](mailto:Olga.Theou@dal.ca); [Kenneth.rockwood@dal.ca](mailto:Kenneth.rockwood@dal.ca)

toxicity of the treatment or the vulnerability of the individual – and using vulnerability as a prod to make the treatments themselves less harmful.

## Ways to Measure Frailty

Frailty has been measured in a variety of ways, with dozens of tools and hundreds of modifications [1, 2]. The most investigated and cited measurement tools are the frailty phenotype and the frailty index (FI), both introduced in 2001 [3, 4]. The frailty phenotype was developed by Linda Fried and colleagues using data from the Cardiovascular Health Study. They identified five key frailty symptoms, including weight loss, fatigue, low grip strength, slow walking speed, and physical inactivity. Based on this tool, frailty has been defined as deficits or impairment in at least three of the five domains, whereas pre-frailty is indicated by impairment in one or two domains. Individuals are considered robust if they do not demonstrate any impairment. Advantages of this syndromic or phenotypic approach include its simplicity and that it has been the most commonly cited and examined among population studies. Disadvantages include the fact that it is hard to include additional performance-based measures in routine care (i.e., grip strength and walking speed) and that it does not readily enable gradation of the degree of frailty. Typically, the phenotype excludes the frailest individuals, who cannot complete the performance-based tests. This tool will not be discussed extensively in this book chapter.

The FI is a health state measure (rather than a specific syndrome), designed to integrate multiple types of health information. It reflects the extent of illness and vulnerability to adverse outcomes and proximity to death [5], and it has been applied in large health databases from many countries (e.g., Canada [6], USA [7, 8], China [9, 10], Sweden [11], and EU [12–14]). An FI can be created from routinely collected clinical or epidemiological information which are then recoded (typically as binary – present/absent) as health deficits using standard criteria [15]. An FI score can be calculated by dividing the number of health deficits present in an individual by the number of health deficits measured. For example, a person with 20 of 40 deficits has an FI score of  $20/40 = 0.5$ , for someone with 10 deficits, the FI is  $10/40 = 0.25$ . Despite variability in the number and nature of deficits recorded in the various databases (e.g., from 30 self-report items to more than 100 items that range from self-report to laboratory and electrocardiographic data [16]), the FI has remarkably consistent characteristics: in population-based datasets, frailty increases exponentially with age (and closely approximates Gompertz law), and it is strongly associated with adverse health outcomes including hospitalization [17], institutionalization, and mortality [16] as well as disease-specific outcomes such as chemotherapy toxicity [18] and cardiac surgery outcomes [19]. Additionally, at any age women have a higher FI than men [20], and there is a demonstrated submaximal limit to the FI at 0.7 beyond which it appears individuals cannot survive [21].

The FI approach has some key advantages. It can be used across many populations and datasets because the nature of the variables included does not matter as long as there are enough of them and they meet some basic criteria. Statistical

weights are not imposed on variables (thus not limiting it to the original dataset that weights were developed in), instead the index self-weights. If more serious health deficits are present (which are each given a value of 1 when present), many more trivial, but related, health deficits will also be present. For example, if congestive heart failure or chronic obstructive pulmonary disease is present, depending on the severity, a person may also have dyspnea, functional impairments, or frequent infections. Further, by capturing information across multiple physiologic systems and transforming this into a continuous measure, the FI therefore allows gradation of severity of frailty. Some disadvantages include the amount of information required, as at least 30 variables should be included. It has been argued that this is arduous to collect from a clinical encounter, though typically these data are easily accessible from routine clinic assessments. For example, the comprehensive geriatric assessment is a fundamental tool in settings serving older adults [22] and can be easily operationalized into an FI as it typically includes 40-60 variables [5]. Also, more recently, it has been proposed that an FI can be constructed by combining commonly used blood tests [23–25]. Another criticism of the FI approach is that different sets of variables are used in different constructions of the FI which is useful epidemiologically, but the clinical implications of variations between FIs in different clinical settings are potentially more unclear.

The FI also greatly reduces the dimensionality of the inquiry. Rather than including each health variable in a statistical model, we can combine them all a single term – the FI. This allows even weak signals – that is, health deficits that individually are not statistically significantly associated with the adverse outcome – to be considered in any FI of 30 or more variables. The accumulation of deficits, even small ones, allows signals to be detected. This is the basis of the FI. Allowing all detected signals to accumulate and not excluding those which fail to meet the criterion of being statistically significant in a multivariable model reflects principles that are well described and commonly employed in bioinformatics [26, 27].

Interestingly, all frailty tools can be analyzed as indices of deficit accumulation. That is, when existing frailty tools are recalculated as the proportion of criteria present of the number that were assessed, the similarities between scales are remarkable [28]. This lends support to the hypothesis that the number of deficits present may be more important than the nature of the deficits in the aging individual. This observation may not be surprising when we consider the heterogeneity of health status in older adults, which nevertheless converges in common pathways characterized by failure of high-order functions, such as mobility, balance, function, social engagement, and cognition. Frailty therefore manifests as progressive disintegration of multiple basic processes, which is the basis of the risk for loss of high-order functions.

## **Mechanisms of Frailty (Deficit Accumulation): Theory**

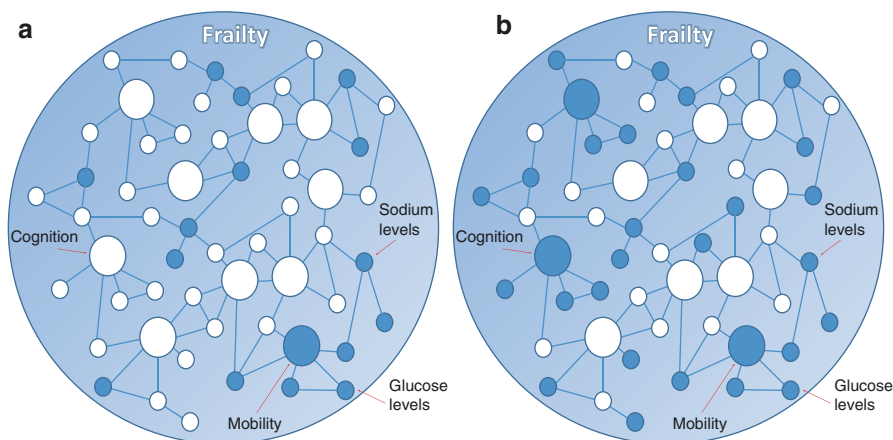
The concept of deficit accumulation is set upon a few tenants that are useful in helping us to understand ageing: as individuals age, they accumulate health deficits. Frailty can be conceptualized as this accumulation of health deficits over time.

With age, our capacity to repair or remove cellular damage becomes impaired, leading to an exponential accumulation of deficits as further insults go unrepaired. Deficits can arise endogenously (e.g., oxidative stress, atherosclerosis) or exogenously (e.g., bone fracture) [29]. Acquiring a deficit (whether exogenous or endogenous) requires a response to either remove or repair the damage caused by the deficit. This largely applies to the subcellular and cellular levels of damage. If we assume that individuals experience insults over the lifetime in a stochastic nature (i.e., randomly determined) at a constant rate on average and take into consideration that unrepaired deficits accumulate exponentially over time, it is clear that the recovery time increases with age [30]. In younger people where recovery time is low, damage from deficits is quickly recovered, whereas older people, where recovery time is higher, may suffer the same number of deficits in a given time period but have a much longer recovery time. As recovery time lengthens, more deficits accumulate [30].

The mechanisms of frailty (deficit accumulation) can be understood in several ways. One might be to study specific protein-protein interactions and then quantify how these change as the degree of frailty changes. This has been done in relation to calcium handling by heart cells in ageing rodents [31, 32]. Another approach is to consider mechanisms at the level of a system. Our group is developing this in a project entitled the “physics of frailty” [33, 34]. There we consider more broadly how deficits develop as they arise from any of the mechanisms associated with ageing. In a network model, we were able to demonstrate that deficits arise as damage propagates through the network’s nodes. Each node can be either undamaged or damaged. Damage to a node is likely to cause damage to the nodes to which they are connected. Mortality arises when the most highly connected nodes in the network become damaged (see Fig. 5.1). The most recent work in these investigations relates the degree of connectivity of a given deficit to its information value. What this means is that some items, such as single laboratory tests, have comparatively low connectivity and therefore low information value, whereas others such as mobility, balance, and cognition and specific instrumental activities of daily living items have high connectivity and information value. This approach allows us to formally address the complexity of the multiple interacting health problems that ultimately are expressed as the degree of deficit accumulation.

Why is recovery time longer with age? This is an area of active inquiry. It has been hypothesized that this occurs due to the diminishing redundancy in recovery systems. Recovery systems in the body are redundant to optimize functioning and delay adverse outcomes. As redundant systems are subjected to damage themselves, there are fewer damage control mechanisms available to repair or remove damage from the deficit.

Overall, “biological ageing” occurs as deficits are acquired and when redundant recovery systems are damaged [30]. Evidence is mounting to suggest that frailty arises over time from these endogenous and exogenous deficits at a subcellular level accumulating to produce cellular deficits, which “scale up” to give rise to deficits at the tissue, organ, and eventually clinically detectable level [35].



**Fig. 5.1** Frailty network of an individual with moderate (left) and severe (right) level of frailty. Each node represents health attributes; bigger nodes represent highly connected attributes (e.g., integrative measures such as mobility and cognition). Smaller nodes represent lower-order more singular functions (e.g., sodium levels). When nodes become damaged (solid blue circles), they contribute to the overall frailty of the network, i.e., the human body. When nodes that are highly connected (the large circles) are damaged, they result in failure of higher-order functions such as cognitive impairment, falls, or even death. Even though the node representing sodium levels itself has few connections, its nearest neighbors are highly connected. In this way, individual deficits can contribute to the damage of the highly connected nodes. This is one way to represent how the impairment of high-order functions such as mobility integrates a lot of information about network damage. Panel (a) represents a network with a moderate degree of frailty; several lower-order nodes have been damaged, and mobility has also become impaired. Panel (b) represents a network with a severe degree of frailty; many lower-order nodes have been damaged, and both mobility and cognition have become impaired

## Mechanisms of Frailty: Evidence

### Hallmarks of Ageing

A 2013 paper on the “hallmarks of ageing” reviewed the literature on common factors of ageing across organisms [36]. The authors argue that altered cellular communication, genomic instability, telomere length, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, and stem cell exhaustion are common factors affected by age-related damage that eventually give rise to clinical problems. This paper put forth a framework for understanding the context of these factors, suggesting that these hallmarks are either primary (those that cause damage), antagonistic (responses to damage, which may work initially but as they are exhausted become deleterious), or integrative (the clinical manifestations of the previous two categories) [36]. This conceptualization endorses a systems perspective, where ageing occurs “due to the interaction between a variety of components” [35]. This review also proposed that the cause of organismal ageing can be essentially reduced to the accumulation of deficits.

Further, it posits that the hallmarks are all so related and interdependent that alteration to one hallmark likely influences the function of others.

## **Telomeres**

In this context, it is worth considering how work on telomeres and frailty has proceeded. Telomeres represent one well-established example of the redundancy in bodily systems as a protection mechanism. Telomeres are essentially caps of non-coding genetic material on the end of chromosomes. With each additional replication (i.e., age), the chromosome shortens, eating into the telomere bit by bit. The long telomere length seen at early ages appears to be a redundant mechanism in place to protect the important genetic material from the deterioration of constant damage with age [36]. Initial studies all demonstrated that frailty indices constructed from self-reported data were not related to telomere length [37]. A later study reported that an FI constructed by combining blood tests was significantly associated with telomere length [38].

## **Animal Models**

For a long time, diseases of ageing (including neuropathological ones) have been studied using animal models that are selected to have few other deficits than the specific one of interest (i.e., 3× or 5× transgenic AD mice). Little of the promising results of mouse work have translated to humans, likely because they ignore the context in which these diseases arise: in ageing individuals with several complex and interacting health problems. Animal models of frailty are new [39]. A rodent FI has been developed based on 31 clinical health deficits including the integumentary, musculoskeletal, ocular, and respiratory systems [40]. This FI was compared and validated against the human FI, and the characteristics were remarkably similar: the FI values in mice were similar to their normalized age categories in humans; slopes of deficit accrual were similar, and the submaximal limit of 0.67 was almost identical [40]. These mouse models serve to advance the biological study of frailty and ageing.

---

## **Frailty and Cognition**

### **Associations**

Frailty is a well-accepted exposure for cognitive decline and dementia, in both cross-sectional and longitudinal analyses [41–50]. Frailty has been associated with age-related cognitive decline [51] as well as development of mild cognitive impairment (MCI) [52] and Alzheimer's disease (AD) [53]. Among people with cognitive impairment, frailty has been shown to predict more rapid and severe decline [52], as well as conversion from MCI to AD [52, 54]. Other reports have demonstrated that change in frailty and cognition were correlated [48, 55, 56]. These observations appear to hold across common confounders including sociodemographic status, sex, and vascular risk factors.

Most studies on cognition and frailty use the frailty phenotype tool, though some issues have arisen with this approach: the measurement and prevalence of frailty using the phenotype are extremely variable [2], and almost all of the individual factors in the frailty phenotype are individually associated with risk for cognitive impairment [3, 54, 57–60]. While this may demonstrate the truly inextricable link between cognition and frailty, it is possible that a frailty tool with few items is not able to wholly represent frailty in the ageing body and therefore overestimate the relationship. To help better understand this, our group created an FI of nontraditional dementia risk factors (i.e., variables that each were not individually associated with dementia), and we found that this measurement of frailty is significantly associated with dementia risk [61, 62] and disease expression [63] after controlling for possible confounders. We have extended these analyses in varied cohorts including the Study of Health and Retirement in Europe [49, 64] and the Honolulu-Asia Aging Study [47, 48]. This suggests that the accumulation of (seemingly) small health issues may combine to give rise to clinically relevant disease outcomes.

Another issue that has been brought up in this literature is the possible inclusion of cognitive variables in the measurement of frailty [65]. While we generally advocate for this, as the brain can be considered another bodily system and the aim of frailty is to capture vulnerability across systems, it will be important for our understanding of the mechanisms of this relationship to measure frailty without cognitive variables so as not to confound the overall relationship.

Overall, this evidence suggests that overall health impacts dementia risk and that frailty and cognitive decline may share pathophysiological mechanisms.

## Possible Mechanisms

Several mechanisms for the relationship between cognition and frailty have been proposed. Both cognitive decline and frailty are strongly associated with age and are thought to be multiply determined [49]. For this reason, many other age-related conditions show possibilities as mediators, but to date no experimental studies have demonstrated causal mechanisms. Based on the current literature, popular hypotheses for shared mechanisms include hormones, neuropathology, chronic inflammation, cardiovascular risk factors, nutrition and microbiome similarities, metabolic byproducts, and mental health. We will briefly review some of these below, though other reports have reviewed them more in depth [66].

Interestingly, at any age women are more likely to have higher FI scores than do men; the deficits which they accumulate are more likely to include dementia [20]. These observations suggest that sex differences including hormones may be a shared underlying mechanism. Estrogen has been linked with cognition. Peri- and postmenopausal women report declines in memory, and hormone replacement therapy ameliorates this decline in many cases, though this appears to be dependent on a critical window of initiation at menopause rather than later in life [67–71] and is not without controversy. Women are at higher risk for common age-related



disease, particularly after menopause, including osteoarthritis, stroke, and diabetes mellitus [20, 72], suggesting that this age-related state may contribute to overall frailty as well.

Evidence has demonstrated that testosterone decreases with age and is associated with reduced muscle mass. In healthy adults, testosterone is thought to promote neuroplasticity and to regulate the accumulation of amyloid-beta in the brain to some extent – though these functions appear to work (and be associated with changes in) with a complex network of hormones. The majority of the evidence for the testosterone mechanism has been done only in men [73]; therefore further studies of the effect of sex hormones (including estrogen) should be undertaken with a mixed sex sample to better understand their contribution.

Alzheimer's disease neuropathology has been linked to both cognition and frailty [74]. Buchman and colleagues reported that a composite measure of Alzheimer's disease type neuropathology (specifically neuritic and diffuse plaques as well as neurofibrillary tangles) was associated with the frailty phenotype in both demented and non-demented individuals [75]. In a later study, this group demonstrated that AD pathology was associated with cognitive baseline and change, as well as phenotypic frailty [55].

Chronic inflammation has been suggested as one of the main culprits for a shared mechanism between cognitive decline and frailty seen in older adults. In humans, acute injury initiates involvement of both local and systemic inflammatory markers that mount a response to repair the injury. If recovery/repair is prolonged, or the inflammation remains to respond to other subclinical issues, inflammation becomes chronic. What starts out as an appropriate response to damage becomes deleterious itself. This chronic inflammatory response (as measured by elevated levels of inflammatory markers such as C-reactive protein) has been associated with both frailty and cognitive decline; further, in women, inflammatory markers actually mediated the relationship between muscle strength and cognition [76].

From a deficit accumulation perspective, it is unsurprising that the exploration of inflammation in relation to frailty and cognition is proving fruitful. Chronic inflammation occurs commonly in ageing and in its deleterious manifestation as “inflammaging” leads to the subclinical accumulation of pro-inflammatory factors that are associated with many illnesses, as well as with frailty [77]. It is one aspect of changes in the immune system with ageing, which, broadly, include less effective adaptive immunity, even as innate immunity remains reasonably intact. Indeed, the distinction between deleterious inflammaging and aspects of immune senescence that can be seen as adaptive [77] is an example of why a fuller understanding of the relationship between deficit accumulation, frailty, and the risk of adverse outcomes may require the evaluation of protective factors (e.g., health beliefs and practices, education, personal resources) either separately [47] or as part of a broadly construed social vulnerability [78, 79].

## **What Comes First: Frailty or Cognitive Decline?**

Multiple observational studies have reported that changes in frailty and cognition are correlated. Some reports demonstrate that frailty leads to cognitive decline [43, 50, 52–54, 63], and others have shown that cognitive decline precedes



subsequent frailty change [48, 49]. Given the common mechanisms, it is unlikely that one predictably causes the other, but rather that they each contribute to a cycle of decline.

---

## **What Do Frailty, Cognitive Decline, and Falls Have to Do with Each Other?**

### **What Is the Mechanism of the Relationship Between Frailty, Cognition, and Falls?**

Although the intersections between falls and cognition, as well as falls and frailty, have been well-studied, very few investigations have looked at all three issues. This is an important area of inquiry as frailty is likely to impact higher-order functions, such as thinking, function, social engagement, and mobility, suggesting they have much in common [80]. The relationship between cognition, mobility, and falls has been extensively discussed in the other book chapters. Here we will mostly focus on the interaction of these two concepts with frailty.

Impaired mobility has been shown to increase severity of frailty, as well as be a consequence of frailty [81]. Further, among studies of frailty (defined phenotypically) and cognition, typically the walking speed domain is most highly related to cognitive decline [52] and frailty [60]. Many studies examined mobility as an indicator or screening tool for frailty assessment [82]. Given that we know that many people with dementia are frail [66], it is important to understand their high risk for falls, and frailty measurement may be able to more accurately predict falls.

Possible mechanisms of this relationship include common neuropathology that can contribute to both cognitive decline and poor gait control. Another possibility is that people with impaired frontal lobe function (particularly disinhibition and lack of insight) may walk too fast for their level of frailty; it has been theorized that fall risk in people with dementia can be partially explained by the loss of gait velocity control [83]. Importantly, people with dementia also demonstrate slower reaction time and higher gait variability [81] increasing their risk for falls. Cognitive distraction also appears to be a common risk: a dual-task cognitive distraction protocol demonstrated that frail older adults had reduced balance complexity when asked to stand and complete a cognitive task than just standing. Authors suggest that this decrease in balance complexity, coupled with the increased demands of a cognitive task, may lower the threshold for falls in frail older adults [84]. The so-called cognitive frailty, which has been defined as the simultaneous presence of both physical frailty and cognitive impairment (not attributable to dementia [85]), has also been suggested to increase risk for falls [83, 86, 87]. Even so, there is debate among researchers about this concept.

Again, because both falls and cognitive decline (as well as frailty) are highly associated with age, many other conditions are also associated with both. Cardiovascular disease, depression, and diabetes mellitus are prominent factors associated with both mobility impairment [88–90] and cognitive decline [91–93].

Underlying mechanisms associated with frailty (e.g., chronic inflammation, or any of the more specific hallmarks of ageing [36]) are known culprits in the

pathophysiology of cognitive decline/dementia and falls, suggesting that frailty interventions may be useful in the prevention and possibly amelioration of symptoms in dementia and falls. Likewise, improved mobility leads to stabilization or improvement of frailty status [94]. Recently, it has been suggested that the relationship between cognitive impairment, mobility impairment and falls, and frailty could be related to underlying processes affecting function in shared brain networks as depicted in Fig. 5.1 [86]. Thus, understanding these relationships as a result of an insult to common brain networks may point to modifiable factors including vascular damage, chronic inflammation, neurodegeneration, or yet to be defined factors [95–97]. It has also been recently shown that microvascular and neurodegenerative changes in brain pathology are independently associated with frailty and cognitive status [55].

Further, some of the mechanisms of the relationship between cognition and frailty extend to mobility impairment and falls; for example, estrogen decrease at menopause has been significantly associated with impaired mobility, falls, and gait velocity, as well as cognitive impairment [98].

### **Why Is It Beneficial to Look at Frailty in People with Dementia and Fallers?**

People with dementia are at high risk of falling. They are typically frail and frequently have impaired mobility, even at early stages [99]. Frail individuals with dementia also demonstrate unsteady gait or hurried walking [81]. Falls in older adults are difficult to predict [81], and frailty may provide a useful risk assessment for people living with cognitive impairment at risk of falling.

Frail people with dementia often live in institutional care. This is thought to be protective, as care workers can monitor and help overcome mobility challenges as well as reduce wandering (which can lead to falls), but issues of autonomy frequently arise. It is important to note the bias in data pertaining to falls: patients who can improve mobility and move more are more likely to fall [100]; therefore we have to carefully consider aims to improving function and quality of life by allowing patients the opportunities to mobilize, even at the possible risk of falls. In many cases such as in frail people residing in long-term care facilities or frail hospitalized patients, falls is not the worst outcome. Importantly, frailty interventions will improve overall risk of falling and improve function and quality of life, but this may reflect bias in the data. Considering goals of care is vital in this pursuit.

### **Interventions to Improve Outcomes and Quality of Life**

Frailty can provide a useful framework for understanding risk and targeting improvement in vulnerability to both falls and cognitive decline. Many have suggested that management of frailty should start in primary care [101]. There, frailty measurement allows simple risk stratification for older adults [102]. This has been operationalized

by using a comprehensive geriatric assessment (CGA; from which an FI can be easily calculated) [5]. While there is some evidence that frailty measurement in primary care contributes to proper care management and improves patient outcomes [103, 104] including reversing frailty levels [105], more randomized-controlled trials are necessary to evaluate this important question [106].

Frailty interventions are still an active area of study, though initial studies have taken a multimodal approach – targeting improvement in mobility (via exercise), sleep quality, nutrition, social engagement, and chronic disease management. Others have primarily focused on exercise interventions; importantly, it has been shown that increased mobility can modify prognosis at any level of frailty [105]. These have been well-regarded as they are cost-effective and easy and can target many aspects of frailty with just one mode of intervention.

---

## Conclusions and Future Directions

It is important to bring some of the essential lessons from studying frailty to bear on the study of cognition and motor function. An essential lesson is that “the problems of old age come as a package” [107]. Even though scientific inquiry has reaped immeasurable benefit from reductionism, the study of age-related phenomena reveals its limitations. Reducing the ills of ageing to single phenomena that are best understood when related factors are “controlled for” in multivariable models, although conventional, is much less rigorous than imagined. We argue here that it is better to situate the problems of old age in a quantitative package as, for example, has been done by quantifying the degree of frailty in an FI [108]. This seems especially promising given the clear links in deficit accumulation across species [109], and the consistency of both subclinical and clinical markers of ageing across the life course [23].

In that light, the fact that there are shared features between risks for decline in cognition and in gait is unsurprising. The question is how we should interpret this information. Can we identify mechanisms that are mutable if dealt with individually? The experience with drugs that modify the processing or accumulation of amyloid in Alzheimer’s disease is a sobering lesson in that. To those who support the single-mechanism approach, the response has been to change who is targeted, in what they imagine must be a form of precision medicine. That only those with the possibility of “target organ engagement” will benefit seems reasonable, but what other factors (not just other genes, but environmental and lifestyle factors) might influence disease risk and expression has received little broad-minded consideration other than now aiming to get at the healthiest, youngest people possible in studies imagined to be “proof of concept.” Given the at least modest success of multifactorial studies [110, 111], some attention should be paid to the incorporation of such approaches in studies that seek to intervene in how frailty and cognitive impairment might be treated, especially when both seen together.

Another lesson concerns the framing of measurement and modeling. Work on frailty has been criticized for being negative in its implications [112]. Whether the best response to this is to consider that an initial negative perception has not held

much back research on cancer, or to simply count assets and not deficits, or consider instead resilience or intrinsic capacity remains equivocal. This is worthy of further consideration. Perhaps a focus on maintaining gait speed across the life course rather than focusing on age-related slowing might be more prudent and promote a more optimistic view of ageing.

## References

1. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, Singh-Manoux A, et al. Measures of frailty in population-based studies: an overview. *BMC Geriatr*. 2013;13:64.
2. Theou O, Cann L, Blodgett J, Wallace LMK, Brothers TD, Rockwood K. Modifications to the frailty phenotype criteria: systematic review of the current literature and investigation of 262 frailty phenotypes in the Survey of Health, Ageing, and Retirement in Europe. *Ageing Res Rev*. 2015;21:78–94.
3. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–57.
4. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001;1:323–36.
5. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med*. 2011;27(1):17–26.
6. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *Can Med Assoc J*. 2011;183(8):E487–94.
7. Arbeev KG, Ukraintseva SV, Akushevich I, Kulminski AM, Arbeeva LS, Akushevich L, et al. Age trajectories of physiological indices in relation to healthy life course. *Mech Ageing Dev*. 2011;132(3):93–102.
8. Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring frailty in medicare data: development and validation of a claims-based frailty index. *J Gerontol A Biol Sci Med Sci*. 2017;73:980.
9. Goggins WB, Woo J, Sham A, Ho SC. Frailty index as a measure of biological age in a Chinese population. *J Gerontol A Biol Sci Med Sci*. 2005;60(8):1046–51.
10. Bennett S, Song X, Mitnitski A, Rockwood K. A limit to frailty in very old, community-dwelling people: a secondary analysis of the Chinese longitudinal health and longevity study. *Age Ageing*. 2013;42(3):372–7.
11. Mitnitski A, Bao L, Skoog I, Rockwood K. A cross-national study of transitions in deficit counts in two birth cohorts: implications for modeling ageing. *Exp Gerontol*. 2007;42(3):241–6.
12. Romero-Ortuno R, Kenny RA. The frailty index in Europeans: association with age and mortality. *Age Ageing*. 2012;41(5):684–9.
13. Theou O, Brothers TD, Rockwood MR, Haardt D, Mitnitski A, Rockwood K. Exploring the relationship between national economic indicators and relative fitness and frailty in middle-aged and older Europeans. *Age Ageing*. 2013;42(5):614–9.
14. Hoogendijk EO, Theou O, Rockwood K, Onwuteaka-Philipsen BD, Deeg DJH, Huisman M. Development and validation of a frailty index in the Longitudinal Aging Study Amsterdam. *Aging Clin Exp Res*. 2017;29(5):927–33.
15. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8(1):24.
16. Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70: LONG-TERM RISK OF DEATH DEFINED BY AGE 70. *J Am Geriatr Soc*. 2006;54(6):975–9.

17. Wallace LMK, Theou O, Kirkland SA, Rockwood MRH, Davidson KW, Shimbo D, et al. Accumulation of non-traditional risk factors for coronary heart disease is associated with incident coronary heart disease hospitalization and death. *PLoS One* [Internet]. 2014 [cited 2015 Apr 12];9(3). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3953643/>.
18. Cohen HJ, Smith D, Sun C-L, Tew W, Mohile SG, Owusu C, et al. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. *Cancer*. 2016;122(24):3865–72.
19. Sepehri A, Beggs T, Hassan A, Rigatto C, Shaw-Daigle C, Tangri N, et al. The impact of frailty on outcomes after cardiac surgery: a systematic review. *J Thorac Cardiovasc Surg*. 2014;148(6):3110–7.
20. Hubbard RE. Sex differences in frailty. *Interdiscip Top Gerontol Geriatr*. 2015;41:41–53.
21. Theou O, Walstonb J, Rockwooda K. Operationalizing frailty using the frailty phenotype and deficit accumulation approaches. *Interdiscip Top Gerontol Geriatr*. 2015;41:66–73.
22. Bakker FC, Olde Rikkert MGM. Hospital care for frail elderly adults: from specialized geriatric units to hospital-wide interventions. *Interdiscip Top Gerontol Geriatr*. 2015;41:95–106.
23. Blodgett JM, Theou O, Howlett SE, Rockwood K. A frailty index from common clinical and laboratory tests predicts increased risk of death across the life course. *GeroScience*. 2017;39:447.
24. Blodgett JM, Theou O, Howlett SE, Wu FCW, Rockwood K. A frailty index based on laboratory deficits in community-dwelling men predicted their risk of adverse health outcomes. *Age Ageing*. 2016;45(4):463–8.
25. Howlett SE, Rockwood MR, Mitnitski A, Rockwood K. Standard laboratory tests to identify older adults at increased risk of death. *BMC Med*. 2014;12(1):171.
26. Dawes RM. The robust beauty of improper linear models in decision making. *Am Psychol*. 1979;34:571–82.
27. Oppenheim AV, Willsky AS. Signals and systems. Upper Saddle River, NJ: Prentice Hall; 1997. 997 p.
28. Theou O, Brothers TD, Peña FG, Mitnitski A, Rockwood K. Identifying common characteristics of frailty across seven scales. *J Am Geriatr Soc*. 2014;62(5):901–6.
29. Rockwood K, Mitnitski A, Howlett SE. Frailty: scaling from cellular deficit accumulation? *Interdiscip Top Gerontol Geriatr*. 2015;41:1–14.
30. Mitnitski A, Song X, Rockwood K. Assessing biological aging: the origin of deficit accumulation. *Biogerontology*. 2013;14(6):709–17.
31. Parks RJ, Fares E, MacDonald JK, Ernst MC, Sinal CJ, Rockwood K, et al. A procedure for creating a frailty index based on deficit accumulation in aging mice. *J Gerontol A Biol Sci Med Sci*. 2012;67A(3):217–27.
32. Moghtadaei M, Jansen HJ, Mackasey M, Rafferty SA, Bogachev O, Sapp JL, et al. The impacts of age and frailty on heart rate and sinoatrial node function. *J Physiol*. 2016;594(23):7105–26.
33. Mitnitski AB, Rutenberg AD, Farrell S, Rockwood K. Aging, frailty and complex networks. *Biogerontology*. 2017;2:1–14.
34. Rutenberg AD, Mitnitski AB, Farrell SG, Rockwood K. Unifying aging and frailty through complex dynamical networks. *Exp Gerontol*. 2017;107:126.
35. Rockwood K, Mitnitski A, Howlett SE. Frailty: scaling from cellular deficit accumulation? 2015 [cited 2015 Oct 23]; Available from: <http://www.karger.com/Article/FullText/381127>.
36. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–217.
37. Saum K-U, Dieffenbach AK, Muezzinler A, Müller H, Holleczeck B, Stegmaier C, et al. Frailty and telomere length: cross-sectional analysis in 3537 older adults from the ESTHER cohort. *Exp Gerontol*. 2014;58:250–5.
38. Bello GA, Chiu Y-HM, Dumancas GG. Association of a biomarker-based frailty index with telomere length in older US adults: findings from NHANES 1999–2002. *bioRxiv*. 2017; <https://doi.org/10.1101/191023>.

39. Kane AE, Ayaz O, Ghimire A, Feridooni HA, Howlett SE. Implementation of the mouse frailty index. *Can J Physiol Pharmacol*. 2017;95(10):1149–55.
40. Whitehead JC, Hildebrand BA, Sun M, Rockwood MR, Rose RA, Rockwood K, et al. A clinical frailty index in aging mice: comparisons with frailty index data in humans. *J Gerontol A Biol Sci Med Sci*. 2014;69(6):621–32.
41. Mitnitski A, Fallah N, Wu Y, Rockwood K, Borenstein AR. Changes in cognition during the course of eight years in elderly Japanese Americans: a multistate transition model. *Ann Epidemiol*. 2010;20(6):480–6.
42. Peters R, Beckett N, Beardmore R, Peña-Miller R, Rockwood K, Mitnitski A, et al. Modelling cognitive decline in the Hypertension in the Very Elderly Trial [HYVET] and Proposed risk tables for population use. *PLoS One* [Internet]. 2010 [cited 2016 Nov 21];5(7). Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2909901/>.
43. Mitnitski A, Fallah N, Rockwood K. A multistate model of cognitive dynamics in relation to frailty in older adults. *Ann Epidemiol*. 2011;21(7):507–16.
44. Panza F, Solfrizzi V, Frisardi V, Maggi S, Sancarolo D, Adante F, et al. Different models of frailty in predementia and dementia syndromes. *J Nutr Health Aging*. 2011;15(8):711–9.
45. Song X, Mitnitski A, Zhang N, Chen W, Rockwood K. Dynamics of brain structure and cognitive function in the Alzheimer's disease neuroimaging initiative. *J Neurol Neurosurg Psychiatry*. 2013;84(1):71–8.
46. Mitnitski AB, Fallah N, Dean CB, Rockwood K. A multi-state model for the analysis of changes in cognitive scores over a fixed time interval. *Stat Methods Med Res*. 2014;23(3):244–56.
47. Armstrong JJ, Mitnitski A, Andrew MK, Launer LJ, White LR, Rockwood K. Cumulative impact of health deficits, social vulnerabilities, and protective factors on cognitive dynamics in late life: a multistate modeling approach. *Alzheimers Res Ther*. 2015;7(1):38.
48. Armstrong JJ, Godin J, Launer LJ, White LR, Mitnitski A, Rockwood K, et al. Changes in frailty predict changes in cognition in older men: the Honolulu-Asia aging study. *J Alzheimers Dis*. 2016;53(3):1003–13.
49. Godin J, Armstrong JJ, Rockwood K, Andrew MK. Dynamics of frailty and cognition after age 50: why it matters that cognitive decline is mostly seen in old age. *J Alzheimers Dis*. 2017;58(1):231–42.
50. Kelaiditi E, Canevelli M, Andrieu S, Del Campo N, Soto ME, Vellas B, et al. Frailty index and cognitive decline in Alzheimer's disease: data from the impact of cholinergic treatment use study. *J Am Geriatr Soc*. 2016;64(6):1165–70.
51. Auyeung TW, Lee JSW, Kwok T, Woo J. Physical frailty predicts future cognitive decline—a four-year prospective study in 2737 cognitively normal older adults. *J Nutr Health Aging*. 2011;15(8):690–4.
52. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc*. 2010;58(2):248–55.
53. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. *Psychosom Med*. 2007;69(5):483–9.
54. Samper-Ternent R, Al Snih S, Raji MA, Markides KS, Ottenbacher KJ. Relationship between frailty and cognitive decline in older Mexican Americans: FRAILTY AND COGNITIVE DECLINE IN OLDER MEXICAN AMERICANS. *J Am Geriatr Soc*. 2008;56(10):1845–52.
55. Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *J Gerontol A Biol Sci Med Sci*. 2014;69(12):1536–44.
56. Brigola AG, Rossetti ES, dos Santos BR, Neri AL, Zazzetta MS, Inouye K, et al. Relationship between cognition and frailty in elderly: a systematic review. *Dement Neuropsychol*. 2015;9(2):110–9.
57. Searle SD, Rockwood K. Frailty and the risk of cognitive impairment. *Alzheimers Res Ther* [Internet]. 2015 [cited 2015 Oct 30];7(1). Available from: <http://alzres.com/content/7/1/54>.



58. Royall DR, Espino DV, Polk MJ, Palmer RF, Markides KS. Prevalence and patterns of executive impairment in community dwelling Mexican Americans: results from the Hispanic EPESE Study. *Int J Geriatr Psychiatry*. 2004;19(10):926–34.
59. Alfaro-Acha A, Al Snih S, Raji MA, Markides KS, Ottenbacher KJ. Does 8-foot walk time predict cognitive decline in older Mexicans Americans? *J Am Geriatr Soc*. 2007;55(2):245–51.
60. Ottenbacher KJ, Ostir GV, Peek MK, Snih SA, Raji MA, Markides KS. Frailty in older Mexican Americans. *J Am Geriatr Soc*. 2005;53(9):1524–31.
61. Song X, Mitnitski A, Rockwood K. Nontraditional risk factors combine to predict Alzheimer disease and dementia. *Neurology*. 2011;77(3):227–34.
62. Song X, Mitnitski A, Rockwood K. Age-related deficit accumulation and the risk of late-life dementia. *Alzheimers Res Ther*. 2014;6:54.
63. Mitnitski A, Fallah N, Rockwood MRH, Rockwood K. Transitions in cognitive status in relation to frailty in older adults: a comparison of three frailty measures. *J Nutr Health Aging*. 2011;15(10):863–7.
64. Sterniczuk R, Theou O, Rusak B, Rockwood K. Sleep disturbance is associated with incident dementia and mortality. *Curr Alzheimer Res*. 2013;10(7):767–75.
65. Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB, Walston JD, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. *J Am Geriatr Soc*. 2004;52(4):625–34.
66. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment—A review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12(4):840–51.
67. Sherwin BB. Estrogen and cognitive functioning in women: lessons we have learned. *Behav Neurosci*. 2012;126(1):123–7.
68. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the women's health initiative memory study: a randomized controlled trial. *JAMA*. 2003;289(20):2651.
69. Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory re-visited. *Ann Neurol*. 2011;69(1):163–9.
70. Bove R, Secor E, Chibnik LB, Barnes LL, Schneider JA, Bennett DA, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology*. 2014;82(3):222–9.
71. Bagger YZ, Tankó LB, Alexandersen P, Qin G, Christiansen C, Group for the PS. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. *Menopause*. 2005;12(1):12.
72. US Preventive Services Task Force, Grossman DC, Curry SJ, Owens DK, Barry MJ, Davidson KW, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2017;318(22):2224–33.
73. Maggio M, Dall'Aglia E, Lauretani F, Cattabiani C, Ceresini G, Caffarra P, et al. The hormonal pathway to cognitive impairment in older men. *J Nutr Health Aging*. 2012;16(1):40–54.
74. Wallace LMK, Theou O, Andrew MK, Rockwood K. Relationship between frailty and Alzheimer's disease biomarkers: a scoping review. *Alzheimers Dement (Amst)*. 2018;10:394.
75. Buchman AS, Yu L, Wilson RS, Schneider JA, Bennett DA. Association of brain pathology with the progression of frailty in older adults. *Neurology*. 2013;80(22):2055–61.
76. Canon ME, Crimmins EM. Sex differences in the association between muscle quality, inflammatory markers, and cognitive decline. *J Nutr Health Aging*. 2011;15(8):695–8.
77. Fulop T, McElhaney J, Pawelec G, Cohen AA, Morais JA, Dupuis G, et al. Frailty, inflammation and immunosenescence. *Interdiscip Top Gerontol Geriatr*. 2015;41:26–40.
78. Andrew MK, Rockwood K. Social vulnerability predicts cognitive decline in a prospective cohort of older Canadians. *Alzheimers Dement*. 2010;6(4):319–325.e1.

79. Wallace LMK, Theou O, Pena F, Rockwood K, Andrew MK. Social vulnerability as a predictor of mortality and disability: cross-country differences in the survey of health, aging, and retirement in Europe (SHARE). *Aging Clin Exp Res*. 2015;27(3):365–72.
80. Rockwood K et al. Reliability of the hierarchical assessment of balance and mobility in frail older adults. *J Am Geriatr Soc*. 2008 - Wiley Online Library [Internet]. [cited 2018 Feb 12]. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2008.01773.x/abstract>.
81. Eeles E, Low CN. Frailty and mobility. *Interdiscip Top Gerontol Geriatr*. 2015;41:107–20.
82. Matsuzawa Y, Konishi M, Akiyama E, Suzuki H, Nakayama N, Kiyokuni M, et al. Association between gait speed as a measure of frailty and risk of cardiovascular events after myocardial infarction. *J Am Coll Cardiol*. 2013;61(19):1964–72.
83. van Iersel MB, Verbeek ALM, Bloem BR, Munneke M, Esselink RAJ, Rikkert MGMO. Frail elderly patients with dementia go too fast. *J Neurol Neurosurg Psychiatry*. 2006;77(7):874–6.
84. Kang HG, Costa MD, Priplata AA, Starobinets OV, Goldberger AL, Peng C-K, et al. Frailty and the degradation of complex balance dynamics during a dual-task protocol. *J Gerontol A Biol Sci Med Sci*. 2009;64(12):1304–11.
85. Kelaiditi E, Cesari M, Canevelli M, Kan GA, van Ousset P-J, Gillette-Guyonnet S, et al. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. *J Nutr Health Aging*. 2013;17(9):726–34.
86. Montero-Odasso MM, Barnes B, Speechley M, Hunter MWS, Doherty TJ, et al. Disentangling cognitive-frailty: results from the gait and brain study. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1476–82.
87. Cognitive frailty: a systematic review of epidemiological and neurobiological evidence of an age-related clinical condition | Rejuvenation Research [Internet]. Mary Ann Liebert, Inc., publishers. [cited 2018 Jun 3]. Available from: <https://www.liebertpub.com/doi/pdf/10.1089/rej.2014.1637>.
88. Dumurgier J, Elbaz A, Ducimetière P, Tavernier B, Alépovitch A, Tzourio C. Slow walking speed and cardiovascular death in well functioning older adults: prospective cohort study. *BMJ*. 2009;339:b4460.
89. Volpato S, Bianchi L, Lauretani F, Lauretani F, Bandinelli S, Guralnik JM, et al. Role of muscle mass and muscle quality in the association between diabetes and gait speed. *Diabetes Care*. 2012;35(8):1672–9.
90. Penninx BW, Leveille S, Ferrucci L, van Eijk JT, Guralnik JM. Exploring the effect of depression on physical disability: longitudinal evidence from the established populations for epidemiologic studies of the elderly. *Am J Public Health*. 1999;89(9):1346–52.
91. Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, et al. Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci*. 2007;62(8):844–50.
92. Breteler MMB, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam study. *BMJ*. 1994;308(6944):1604–8.
93. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J*. 2012;42(5):484–91.
94. Fallah N, Mitnitski A, Searle SD, Gahbauer EA, Gill TM, Rockwood K. Transitions in frailty status in older adults in relation to mobility: a multi-state modeling approach employing a deficit count. *J Am Geriatr Soc*. 2011;59(3):524–9.
95. Sorond FA, Cruz-Almeida Y, Clark DJ, Viswanathan A, Scherzer CR, De Jager P, et al. Aging, the central nervous system, and mobility in older adults: neural mechanisms of mobility impairment. *J Gerontol A Biol Sci Med Sci*. 2015;70(12):1526–32.
96. Montero-Odasso M, Annweiler C, Hachinski V, Islam A, Yang N, Toma N, et al. Vascular burden predicts gait, mood, and executive function disturbances in older adults with mild cognitive impairment: results from the gait and brain study. *J Am Geriatr Soc*. 2012;60(10):1988–90.
97. Buchman AS, Yu L, Boyle PA, Levine SR, Nag S, Schneider JA, et al. Microvascular brain pathology and late-life motor impairment. *Neurology*. 2013;80(8):712–8.



98. Shepherd JE. Effects of estrogen on cognition, mood, and degenerative brain diseases. *J Am Pharm Assoc.* 2001;41(2):221–8.
99. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, et al. Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc.* 2008;56(7):1244–51.
100. Barker AL, Nitz JC, Low Choy NL, Haines TP. Mobility has a non-linear association with falls risk among people in residential aged care: an observational study. *J Physiother.* 2012;58(2):117–25.
101. Lacas A, Rockwood K. Frailty in primary care: a review of its conceptualization and implications for practice. *BMC Med.* 2012;10(1):4.
102. Romero-Ortuno R. Frailty in primary care. *Interdiscip Top Gerontol Geriatr.* 2015;41:85–94.
103. Bandinelli S, Lauretani F, Boscherini V, Gandi F, Pozzi M, Corsi AM, et al. A randomized, controlled trial of disability prevention in frail older patients screened in primary care: the FRASI Study. Design and baseline evaluation. *Aging Clin Exp Res.* 2006;18(5):359–66.
104. Li C-M, Chen C-Y, Li C-Y, Wang W-D, Wu S-C. The effectiveness of a comprehensive geriatric assessment intervention program for frailty in community-dwelling older people: a randomized, controlled trial. *Arch Gerontol Geriatr.* 2010;50(Suppl 1):S39–42.
105. Theou O, Park GH, Garm A, Song X, Clarke B, Rockwood K. Reversing frailty levels in primary care using the CARES model. *Can Geriatr J.* 2017;20(3):105–11.
106. Metzelthin SF, van Rossum E, de Witte LP, Ambergen AW, Hobma SO, Sipers W, et al. Effectiveness of interdisciplinary primary care approach to reduce disability in community dwelling frail older people: cluster randomised controlled trial. *BMJ.* 2013;347:f5264.
107. Fontana L, Kennedy BK, Longo VD, Seals D, Melov S. Medical research: treat ageing. *Nature.* 2014;511(7510):405–7.
108. Mitnitski A, Howlett SE, Rockwood K. Heterogeneity of human aging and its assessment. *J Gerontol A Biol Sci Med Sci.* 2016;72:877. <https://doi.org/10.1093/gerona/glw089>.
109. Rockwood K, Blodgett JM, Theou O, Sun MH, Feridooni HA, Mitnitski A, et al. A frailty index based on deficit accumulation quantifies mortality risk in humans and in mice. *Sci Rep* [Internet]. 2017 Feb 21 [cited 2017 May 6];7. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5318852/>.
110. Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet.* 2015;385(9984):2255–63.
111. Ballard C, Corbett A, Orrell M, Williams G, Moniz-Cook E, Romeo R, et al. Impact of person-centred care training and person-centred activities on quality of life, agitation, and antipsychotic use in people with dementia living in nursing homes: a cluster-randomised controlled trial. *PLoS Med.* 2018;15(2):e1002500.
112. Mudge AM, Hubbard RE. Frailty: mind the gap. *Age Ageing* [Internet]. [cited 2018 Feb 12]; Available from: <https://academic.oup.com/ageing/advance-article/doi/10.1093/ageing/afx193/4781624>.

---

## Part II

## Assessments

# Comprehensive Falls Assessment: Cognitive Impairment Is a Matter to Consider

## 6

Olivier Beauchet and Manuel Montero-Odasso

It takes a child one year to acquire independent movement and ten years to acquire independent mobility. An old person can lose both in a day.

Bernard Isaacs [3]

---

### Introduction

This quote from the late Professor Bernard Isaacs, now three decades after being written, still portrays the crude consequence that an older adult (aged 65 and over) may experience after a fall [3]. A fall is usably defined as an event resulting in a person coming to rest unintentionally on the ground or at a lower level [4]. Recurrence is defined as two or more falls in a 12-month period [4]. Falling is a frequent geriatric event mostly caused by mobility impairment (i.e., gait and/or balance impairment) leading to further motor deconditioning in older adults.

---

O. Beauchet

Faculty of Medicine, McGill University, Montreal, QC, Canada

Department of Medicine, Division of Geriatric Medicine, Sir Mortimer B. Davis – Jewish General Hospital and Lady Davis Institute for Medical Research, McGill University, Montreal, QC, Canada

M. Montero-Odasso (✉)

Departments of Medicine (Geriatric Medicine), and Epidemiology and Biostatistics, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada

Gait and Brain Lab, Parkwood Institute, Lawson Health Research Institute, London, ON, Canada

e-mail: [mmontero@uwo.ca](mailto:mmontero@uwo.ca)

**Table 6.1** Frequent consequences of the fall syndrome in older people

Cause	Consequence
Medical	Hematoma
	Fracture
	Chronic pain
	Death
Psychological	Fear of falling
	Anxiety
	Loss of confidence
	Depression
Social	Dependency
	Isolation
	Placement in long-term care
Functional	Immobility
	Deconditioning
	Disability and dependence

Source: Adapted with permission from Montero-Odasso [73]

Falls in older adults are a major public health concern because [3–5] (1) they have a high prevalence and incidence (e.g., up to 30% of older adults fall each year, with increased risk in cognitively impaired individuals), (2) they negatively impact an individual’s health (e.g., hip fractures) and quality of life (e.g., social withdraw), and (3) they impose a high financial burden on the health care system [5]. Table 6.1 summarizes the consequences after falling.

In cognitively impaired individuals there is a greater risk for falls and fall-related injuries, more than doubled compared with cognitively healthy individuals [6, 7]. Moreover, major neurocognitive disorders are strongly associated with falls and their adverse outcomes [6–8]. However, the nature of the interactions between neurocognitive disorders and the other risk factors for falls and fall-related injuries are still a matter of study [9–11].

There is evidence that falls incidence can be reduced by about 20% in community-dwelling older adults [4, 12, 13]. However, interventions are most effective when targeted toward individuals at risk for falls and/or for fall-related injuries [4, 12, 13].

### Comprehensive Falls Assessment

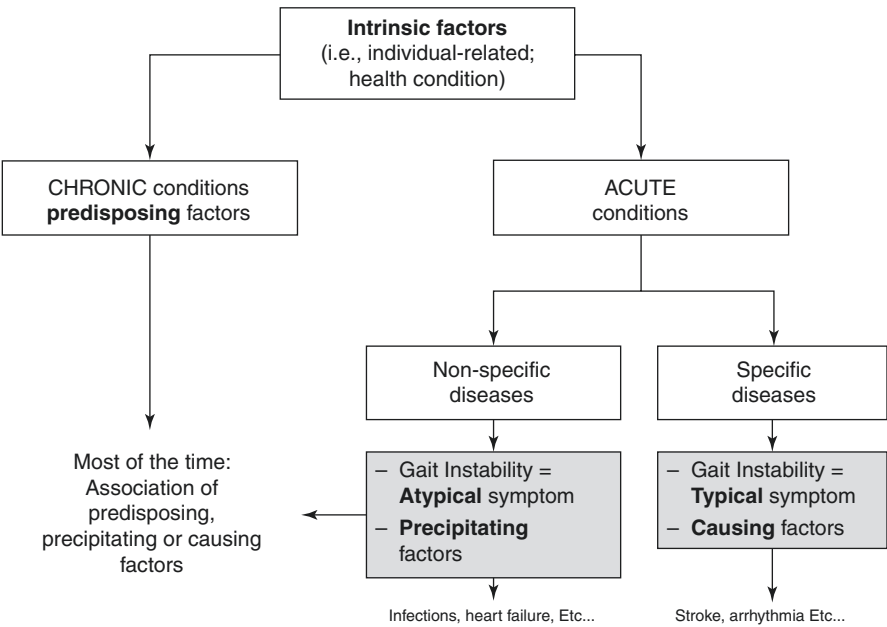
Falls are usually multifactorial in origin and require a comprehensive assessment to determine contributing factors and targeted interventions [4, 14]. Most falls are due to an accumulation of risk factors categorized as intrinsic (individual-related; e.g., gait and/or balance impairment), extrinsic (environment-related; e.g., poor lighting of place of living), and behavioral factors (activity-related such as standing on a chair or using ladders inappropriately) [15–18].

Falls in older adults most commonly occur while walking and/or while standing up from a sitting position, which are both dynamic balance conditions [4, 14]. Thus, gait and balance (intrinsic) disorders are the most common cause of falls in older adults. Most changes in gait and balance that occur in aging are related to

physiological aging of the sensorimotor system combined with adverse consequences of chronic and acute medical conditions [3, 8, 14]. There are complex synergistic interactions between factors provoking gait and balance instability, which may explain why gait and balance instability fluctuate with time [4]. Figure 6.1 summarizes the main intrinsic factors causing gait and/or balance disorders, which may be divided into three categories [19–25]:

- Predisposing factors which are individually related and result from adverse consequences of physiological aging of the sensorimotor system combined with chronic medical conditions leading to chronic gait and balance instability.
- Precipitating factors which are acute medical conditions where gait and/or balance impairment as well as falls are the only presenting symptoms and described as “atypical presentation” of a disease, such as an individual with an “acute pneumonia” whose clinical presentation at the emergency room is with acute gait disturbances and falls.
- Causal factors which also include acute medical conditions but where gait and/or balance impairment as well as falls are typical outcomes, such as an acute stroke affecting gait and balance.

Previous studies showed that the incidence of falls increases consistently as the number of risk factors increase [16, 20, 21, 23]. While modifying only one of these risk factors may reduce incidence of falls, the risk reduction is likely to be greater when multiple risk factors are modified [26]. From a clinical point of view, it is more efficient to select interventions that simultaneously address several risk



**Fig. 6.1** Classification of intrinsic contributing factor for falls

factors. This chapter proposes an aggregation of risk factors into four domains related to potential interventions: (i) central and peripheral nervous system and neuromuscular problems, (ii) medical problems, (iii) environmental problems, and (iv) cardiovascular problems. Table 6.2 lists these domains as well as their proposed risk factors, assessment measures, and tests and some potential interventions appropriate for each giving disorder.

**Table 6.2** Cause of falls according to risk factor identification and grouped regarding potential management based on observational and trial evidence

Domain assessed	Risk factor/disease	Level of evidence <sup>a</sup>	Screen/assessment	Management
Central and peripheral nervous system/neuromuscular	Parkinsonism syndrome Balance and gait problems Lower extremity weakness	Ia Ia Ia	Gait velocity test Get Up and Go POMA	1. Supervised programs (structural gait retraining, balance, transfer and mobility interventions, progressive limb strengthening and flexibility exercises) 2. Provision of appropriate walking aids when needed 3. Vitamin D supplementation
Medical	Dizziness or vertigo Visual impairment Peripheral neuropathy Psychoactive medication/alcohol Hip problems or deformity Cognitive problems or depression	II Ib for cataracts III for visual acuity n/a Ia n/a III	History and examination, including review of drugs, visual acuity assessment, echocardiograph, short Geriatric Depression Scale CAGE questionnaire	1. Appropriate investigation and management of untreated medical problems 2. Review and modification of psychotropic drugs, other culprit drugs, and polypharmacy. Alcohol counselling if indicated 3. Optical correction by an optician or referral to an ophthalmologist 4. Formal psychogeriatric assessment
Environmental	Environmental fall hazards Footwear Multifocal eyeglasses	Ia III II	Occupational therapy: assessment of environmental fall hazards using a standard checklist Check footwear	1. Home hazard modification using standard protocol 2. Advise to wear well-fitting shoes of low heel height and high surface contact 3. Avoid multifocal eyeglasses while walking

**Table 6.2** (continued)

Domain assessed	Risk factor/ disease	Level of evidence <sup>a</sup>	Screen/assessment	Management
Cardiovascular	Orthostatic hypotension Postprandial hypotension Vasovagal syndrome Carotid sinus hypersensitivity	Ia Ib Ia Ib	Cardiac evaluation including heart rate, morning orthostatic blood pressure, and carotid sinus massage supine and tilted upright, prolonged head-up tilt, if indicated	1. Advice on avoiding precipitants and modification of drugs 2. Postural hypotension: compression hosiery, fludrocortisone, or midodrine 3. Cardioinhibitory carotid sinus hypersensitivity: permanent pacemaker 4. Symptomatic vasodepressor carotid sinus hypersensitivity or vasovagal syncope: fludrocortisone or midodrine

Source: Adapted with permission from Montero-Odasso [73]

<sup>a</sup>Level of evidence based on reference [59] as following: class Ia, evidence from at least two randomized controlled trials; Ib, evidence from one randomized controlled trial or meta-analysis of randomized controlled trials; II, evidence from at least one nonrandomized controlled trial or quasi-experimental study; III, evidence from prospective cohort study; IV, based on expert committee opinion or clinical experience in absence of other evidence

Medications are an important precipitant of falls, included in Table 6.2 under medical problems. While there are inherent difficulties in studying the role of medication as a risk factor for falls, there already exists strong evidence that both the type and class of medication, in particular psychotropic agents, sedatives, and vasodilators, and the total number of medications taken can be important causes of falls in older adults [27–30]. vA detailed role of medications and fall risk in cognitively impaired populations is reviewed in Chap. 9.

**Cognitive Aspects of Falls Risk, Gait, and Dual-Task Gait**

Neurocognitive disorders, listed under medical problems (Table 6.2), have been recognized as a key intrinsic risk factor for falls and fall-related injuries [6–8, 31–33]. Cognition and locomotion are two human abilities controlled by the brain [34–36], and with aging, even simple and unobstructed walking relies on high brain levels of gait control at subcortical and cortical levels.

## Cognition

Neurocognitive disorders will increase their prevalence and incidence with the aging population. For instance, in Canada, approximately 15% (747,000) of Canadians aged 65 and over were living with major neurocognitive disorders (i.e., mild to moderate dementia) in 2012 [37], a number that is estimated to increase to 1.4 million in 2031 [37]. The incidence of falls in older adults with neurocognitive disorders is more than doubled compared with cognitive healthy older adults (i.e., 20% versus 40%) [6–8, 38]. The risk of fall-related injuries, regardless of their severity, is also higher in cognitively impaired fallers (around 65%) compared to those cognitively healthy (40%) [31–33].

Most of the existing research, which examines the risk factors for falls in older adults with neurocognitive disorders, has focused on older adults with an established dementia diagnosis at moderate to severe stages [8, 31]. These studies report that both the severity and the type of cognitive impairment are factors that increase the risk for falls. Neurocognitive disorders at moderate to severe stages may be associated with extrapyramidal symptomatology (i.e., bradykinesia, rigidity, otherwise unexplained gait and posture impairment), which explains in part the gait instability and the increased risk for falls and fall-related injuries. Few studies have examined the risk factors for falls and fall-related injuries at the onset of neurocognitive disorders (i.e., mild cognitive impairment and mild dementia) when the extrapyramidal signs are absent and, thus, cannot explain the increased risk for falls. These studies are reviewed in Chap. 12.

## Gait

Dementia-related gait changes have been described, mostly when comparing subjects with Alzheimer's disease (AD) with cognitively healthy control subjects. Walking speed decreases in Alzheimer's disease, and further its decline parallels severity of the disease [39–41]. This change in speed has been related to a decrease in stride length and an increase in support time [41]. Similarly, older adults with vascular cognitive impairment and dementia with Lewy bodies walked more slowly and presented a reduced step length than older adults with AD [42, 43]. Dementia-related gait changes are thought to be not specific to any dementia sub-type [44].

The origins of dementia-related gait changes are not only associated with classic motor disorders of the basal ganglia, cerebellum, and primary motor areas but also central misprocessing of information and related attention and executive functions [45] that are required to maintain a safe gait [46]. Most studies exploring dementia-related gait changes have focused on mean values of stride parameters [40, 44]. An increase in stride-to-stride variability while usual walking and dual-tasking has been shown to be more specific than any change in mean value in patients with dementia [46–50]. This stride-to-stride variability is a finely tuned marker of gait control and, thus, highlights that gait should not be considered as a simple automatic motor behavior but a rather complex and higher level of cognitive functioning [49–51]. Exploring stride-to-stride variability represents a way to access gait disorders



related to higher levels of gait control impairment. Gait variability is treated with detail in Chap. 7 in the “Fundamentals Section” of this book.

Walking is classically described as an automatic, rhythmic, and regular motor activity characterized by alternated, coordinated movements of crossed flexion-extension of the lower limbs while steady-state walking [52]. It is considered as a simple motor activity in healthy older adults because of its predominantly automatic character acquired during the simultaneous maturation of the locomotor and nervous systems. From a neurological viewpoint, the acquisition of such automatic behaviours relies on motor procedural memory, allowing for the gradual appearance of motor processes enabling the automation of walking. Motor procedural memory handles information based on action rules. Its expression is implicit and cannot be dissociated from action. The procedural learning of walking enables the automatic, unconscious triggering of underlying motor programs in healthy adults. Such an implicit character is predominant in walking and suggested that walking only requires limited attentional resources in healthy older adults [53, 54]. Although this assumption has been confirmed in young subjects, several studies proved it was not the case in older adults and, specifically, in older adults with dementia, whose cortical gait control (related to cognitive functions) is importantly involved even in routinely walking [34–36, 49].

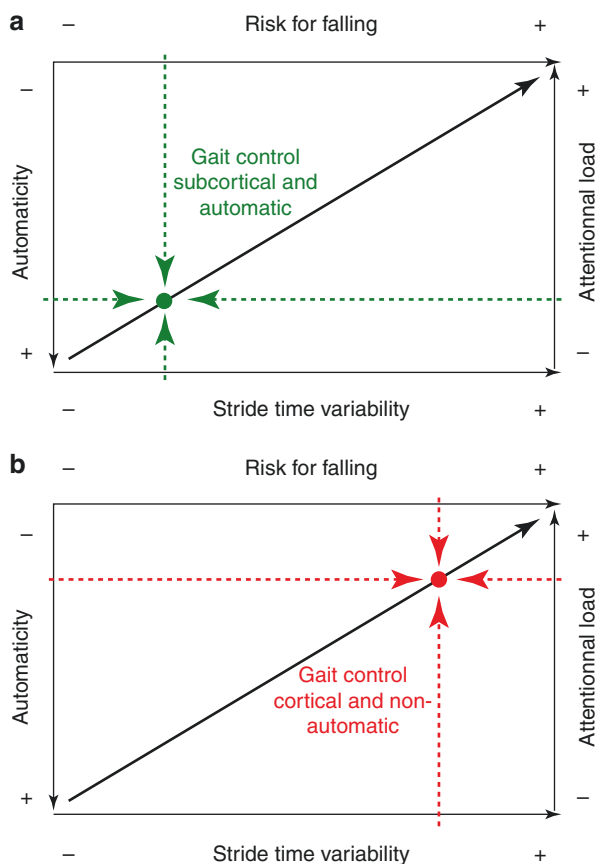
### Dual-Task Paradigm

A clinical test used to highlight cognitive involvement in gait control is based on a dual-task paradigm, where the individual performs an attention-demanding task while walking with any walking change is compared to the reference task, i.e., usual walking alone [36, 55–57]. Dual-task paradigms are based on the hypothesis that two simultaneously performed tasks interfere if relying on identical functional and/or cerebral subsystems. In the case of walking while performing an attention-demanding task, the interference is based on the hypothesis of a joint involvement of attention [55]. The interferences observed are modifications of the performance in one or both tasks, which are measured by comparing the performances under single- and dual-task conditions.

Dual-task-related gait changes reflect the capacity to appropriately allocate attention between two tasks performed simultaneously, to rapidly shift between tasks, and, therefore, are related to executive function efficiency [50, 51, 53–55]. Alzheimer’s individuals with moderate dementia and executive dysfunction present high gait variability suggesting that this gait parameter could be a sensitive and specific marker of frontal cortical control of walking [50, 51].

Figure 6.2 describes how, when attentional demands are increasing, walking relies more on high cognitive control. A safe gait is associated with more automatic control involving low level of attention and characterized by low gait variability. When attentional demands increase or when attentional reserve decreases, gait control is less automatic, involves a higher level of attention, and is characterized by high gait variability.

**Fig. 6.2** The interplay between gait performance, gait variability, attentional load, and risk of falls. *Note:* Green point in figure (a) represents a more automatic gait which is associated with more automatic control involving low level of attention and characterized by low gait variability. Red point in figure (b) represents a more instable gait that may occur when control relies more on high level of attention and executive function and is characterized by high gait variability



## Falls Classification and the Value of Gait Assessment

Falls can be classified in a number of diverse ways including by their number (single fall versus multiple falls), whether or not an injury was sustained (injurious falls vs. non-injurious falls), and what type of risk factors may have been involved (intrinsic vs. extrinsic factors). The traditional classification, based on the presence of intrinsic and extrinsic factors, has been validated and accepted worldwide [23]; however, to attribute a fall fully to an extrinsic factor can be difficult as the majority of environmentally related falls result from an interaction with the intrinsic factors of that individual. Although the intrinsic-extrinsic categorization was originally intended to separate and identify multiple contributors to the fall, older people who experience an extrinsic fall often have an underlying intrinsic condition that decreases their ability to compensate for the hazardous situation. In other words, there may be an intrinsic incapacity to avoid the external factors. As explained earlier, falls are often related to a complex interaction among these factors that can challenge postural control and the ability of the individual to maintain an upright position.

## Gait Assessment

Gait is a complex task that depends on the normal functioning of multiple systems working in a highly coordinated and integrated manner [58–62]. Gait is a dynamic balance condition in which the body's center of gravity is located above a small base of support while it moves in the horizontal plane [63]. As long the center of gravity is maintained over the base of support, gait is stable [64]. To maintain postural stability while walking, an individual is therefore required to actively control the movements of their center of gravity [63, 64]. Several physiological sensory and motor subsystems contribute to the dynamic postural control, the most important ones identified in older adults being muscle strength, lower limb proprioception, vision and hearing, and cognition [8, 17–19]. Age-related physiological impairment in the performance in these five subsystems may, therefore, modulate gait performance.

As impairments in different domains can alter these delicate systems, it has been hypothesized that different chronic conditions such as visual or hearing problems, muscular weakness, osteoarthritis, or peripheral neuropathy could be evidenced through gait performance [62]. In addition, certain psychotropic medications such as benzodiazepines and neuroleptics, which have central nervous system action, may also affect gait performance. Therefore, gait performance can be seen as a common pathway affected by different factors that can cause falls. This fact may explain why gait problems “*per se*” are among the highest predictive risk factor for falls in older adults [62, 63].

In clinical practice, single and rare diseases that cause gait problems in older people (such as myelopathy or normal pressure hydrocephalus) are important to recognize, as they require specific treatment, but they are not prevalent. Rather, common conditions including acute and chronic pain, severe knee osteoarthritis, parkinsonism, or just muscle weaknesses due to deconditioning, are prevalent causes of gait problems. Clinical observation can detect important gait problems in the majority of older adults, so formal testing in a gait laboratory is not necessary for everyone. However, this kind of high-tech analysis might be useful in particular cases or for developing specific rehabilitation strategies, measuring changes in gait quantitative markers, and for research purposes. A focused and careful observation of the gait performance can detect subtle abnormalities, underlying impairments, and the pathologic process involved. Table 6.3 describes some of the common causes of falls and gait problems in older adults and their relation to performance-based evaluation.

Operationally, the underlying impairments in gait can be grouped into three major hierarchical categories based on the sensorimotor level involved, as outlined in Table 6.4. Nutt and Alexander have proposed this classification of gait disorder based on sensorimotor levels coining the term “lower-level gait disorders” to refer to an altered gait that is a result of lower extremity problems or peripheral dysfunction [44, 52]. This impairment can be attributed to joint and/or muscular problem as well as to a peripheral nervous system disease. Lower extremity motor problems are prevalent in older adults and can lead to compensatory changes in gait as a result of

**Table 6.3** Common causes of falls and abnormal mobility and gait in older adults in relation to performance-based evaluation

Symptom	Potential cause
Difficulty rising from a chair	Weakness
	Osteoarthritis
Instability on first standing	Hypotension
	Weakness
Instability with eyes closed	Problems related to proprioception
Decreased step height/length	Parkinsonism
	Frontal lobe disease
	Fear of falling

Source: Adapted with permission from Montero-Odasso [73]

**Table 6.4** Common cause of gait disorder in older people according to the hierarchic level

Level	Deficit/condition	Gait characteristic
Low	Peripheral sensory ataxia: posterior column, peripheral nerves, vestibular and visual ataxia	Unsteady, uncoordinated (especially without visual input)
	Peripheral motor deficit due to hip problems	Avoids weight bearing on affected side
	Arthritis (antalgic gait, joint deformity)	Painful knee flexed Painful spine produces short slow steps, and decreased lumbar lordosis, kyphosis, and ankylosing spondylosis produce stooped posture
	Peripheral motor deficit due to myopathic and neuropathic conditions (weakness)	Proximal motor neuropathy produces waddling and foot slap Distal motor neuropathy produces distal weakness
Middle	Spasticity from hemiplegia, hemiparesis	Leg swings outward and in a semi-circle from hip (circumduction)
	Spasticity from paraplegia, paresis	Circumduction of both legs; steps are short, shuffling, and scraping
	Parkinsonism	Small shuffling steps, hesitation, acceleration (festination), falling forward (propulsion)
	Cerebral ataxia	Wide-based gait with increased trunk sway, irregular stepping
High	Cautious gait	Fear of falling with appropriate postural responses, normal to widened gait base, shortened stride, slower turning en bloc. Performance improves with assistance or evaluator walking on the side
	Ignition failure	Frontal gait disorder: difficulty initiating gait; short, shuffling gait, like Parkinsonian, but with a wider base, upright posture, and arm swing presence

Source: Adapted with permission from Nutt, et al. [26] and Alexander [29]

chronic pain, joint and foot deformities, or focal muscle weakness. Using this approach, Hough and colleagues have found that at least 50% of ambulatory elderly seeking a consultation for gait impairment have joint or muscle problems in the lower limbs [64]. A systematic review of the literature found that lower limb muscle weakness is significantly associated with falls and subsequent disability in older adults [65].

Middle sensorimotor level problems are, in general, affecting the modulation of sensory and motor control of gait without affecting the gait ignition. Typical examples are the gait disturbances due to Parkinson's disease or due to spasticity secondary to hemiplegia. High sensorimotor level problems are related, cognitive dysfunction, attentional problems, and fear of falling affecting gait stability or symmetry. This category includes "frontal gait" problems, "ignition gait" disturbances, and the "cautious gait" due to fear of falling. Finally, combinations of these levels are frequently found in clinical practice as older adults may have deficits at more than one sensory-motor level.

Among those older adults who do have a gait disturbance, the cause may be easily identifiable (e.g., Parkinson's disease or previous stroke with hemiparesis); however, there are many older adults with an impaired gait for whom there does not appear to be a well-defined disease. Seminal studies from Sudarsky and colleagues and Bloem and colleagues found that in older adults attending to the neurology clinic, the cause of the gait disturbance was frequently "unknown" even after neuroimaging, in about 10–20% of older adults with a disturbed gait and that up to 11% of the individuals had an idiopathic "senile gait disorder," that is to say a gait disorder of unknown origin [66, 59]. Interestingly, subjects with a gait disorder of unknown origin had a higher risk of falls, fractures, hospitalizations, and mortality after a 2–3 year follow-up period, compared to a group of age-matched subjects with a normal gait [67].

An additional value of gait assessment is to help rule out syncopal falls. It has been postulated that falls secondary to neurally mediated cardiovascular causes may be expressed by a different mechanism, without necessarily chronically affecting gait performance [68]. Although the exact mechanism by which neurally mediated cardiovascular problems cause a fall remains unclear, there is growing clinical evidence for its association with unexplained falls [69]. Therefore, the absence of gait problems in older adults with recurrent falls raises the consideration of syncopal causes of falls [70]. Some patients might not recall losing consciousness, making review of the circumstance of falls with a reliable witness obligatory.

## Dual-Task Gait Assessments

As previously discussed in this chapter, dual-task gait has been proposed and used as a tool to detect the role of cognitive deficits on gross motor performance, gait stability, and navigation, and for falls risk stratification. Specifically, dual-task gait performance isolates the role of attention and executive function deficits in the regulation of brain gait control in older adults [36, 53–56]. Emerging evidence is

sustaining that “dual-task gait” can act as a stress test to the brain to detect impending mobility problems and risk of falls even in individuals without previous falls [36]. The role of dual-task costs as a marker of future falls has been evaluated with mixed results in the literature due to the heterogeneity of studies, small sample sizes, limited prospective fall ascertainment, and the lack of standardization in dual-task procedures [36]. Although clinically meaningful cut-off values of dual-task costs for predicting falls are still controversial and other unanswered questions remain, a growing body of evidence supports the potential clinical utility of this paradigm for falls prediction: it is neither costly nor invasive, can easily be implemented, and provides a valid and sensitive means of assessing motor-cognitive interactions and fall risk. Based on recent studies, a dual-task cost higher than 20% may denote individuals at higher risk of falls even when they sustain a gait speed of 95 cm/s or faster, highlighting the sensitivity and added predictive ability in older adults who have a relatively normal gait speed [71]. A systemic review and meta-analysis done by Lord and colleagues was not able to find the additional value of dual-task gait to predict falls over single gait speed. A systematic review conducted by Muir-Hunter and colleagues found that in the few studies where both single gait and dual-task gait were assessed, dual-task gait showed added value in predicting future falls [72].

---

## **Comprehensive Assessment: Who to Assess? How to Assess?**

Clinical assessment should be separated into two main parts: global and analytic clinical assessment.

The global assessment begins with observing individuals as they rise from a chair or as they walk into the examination room with the aim to detect gait and balance difficulties. The use of a walking aide and its nature (i.e., cane, walker, personal assistance, and supervision) should be noted, and the individual should be asked about his/her subjective perception of gait and balance difficulties using a single question, “Do you have any difficulty walking?,” with a graduated answer (i.e., never, almost never, sometimes, often, and very often).

This visual observation should be complemented with three standardized motor tests providing an objective and quantitative measure of gait and balance performance: the Timed Up and Go (TUG) test, the Five Times Sit to Stand (FTSS) test, and the gait speed (distance divided by ambulation time) when walking a distance of 4 to 6 meters at a steady-state pace. The TUG measures in seconds the time it takes an individual to rise from a chair, walk a distance of 3 meters, turn, walk back to the chair, and sit down. This test has been used extensively in geriatric medicine to examine balance, gait speed, and functional ability that would be required for the performance of basic activities of daily living in older people. A score  $\geq 20$  seconds should be considered as an abnormal performance; however, in high functional older adults, scores of 12 to 15 seconds have been associated with risk of falling. The FTSS measures in seconds the time it takes an individual to stand up from a chair five times as quickly as possible. This clinical test explores postural

control and lower limb muscular strength. A score  $\geq 15$  seconds should be considered as an abnormal performance. Walking speed is a simple, objective, performance-based measure of lower limb neuromuscular function which not only allows detection of subtle impairments and preclinical diseases, but also is a sensitive marker of functional capacity in older adults. A gait speed at usual pace under 1 m/s should also be considered as abnormal.

The analytic clinical assessment involves gathering information from individuals. Demographic (i.e., age in years and sex) and anthropometric items (height in meters [m], weight in kilograms [kg], body mass index (BMI) in  $\text{kg}/\text{m}^2$ ) should be systematically assessed because each may influence gait and balance stability. In addition, the place of living should be considered as a binary variable such as home versus institution: an institutionalized individual should be considered to have a higher risk of gait and balance disorders.

Given that the burden of disease can influence gait and balance performance, it is important to assess this information as well. Different scales have been developed to score morbidity burden, but they remain difficult to use in clinical routine among older adults, especially because of possible recall bias in individuals with cognitive disorders, and lack of feasibility in daily practice. Medication data, including the number of drugs taken daily, provides a global measure of morbidity status and has been associated with physician-rated disease severity as well as with individual-rated health status. Hence, recording the use of medications in the clinical assessment is required. Polypharmacy is defined as use of more than four different medications per day. The use of psychoactive drugs (i.e., benzodiazepines, antidepressants, neuroleptics) needs to be specially recorded, as they are known risk factors for falls. Use of over the counter, recreational (alcohol, cannabis), and illicit drugs should also be reviewed.

Information about falls, with a fall being defined (as per World Health Organization) as an event resulting in a person coming to rest unintentionally on the ground or at another lower level, not as the result of a major intrinsic event (i.e., seizure or syncope) or an overwhelming hazard (i.e., car accident), in the previous 12-month period before the assessment, should be recorded. Information on falls recurrence (i.e.,  $\geq 2$  falls) and severity/injury (see below for more information) should also be noted.

Fear of falling using the single question, "Are you afraid of falling?," with a graded answer (i.e., never, almost never, sometimes, often, and very often) should be asked to the patient as fear of falling is associated with a greater gait and/or balance instability.

Collecting information on disorders or diseases that directly influence gait performance is also recommended. First, information on neurological disease (limited to the existence or non-existence of dementia) and other diseases (coded as yes or no) should be collected. Information on memory complaints, MCI, nature of dementia (i.e., Alzheimer's disease, non-Alzheimer's disease neurodegenerative dementia, vascular cognitive impairment, mixed dementia), Parkinson disease, idiopathic normal pressure hydrocephalus, cerebellar disease, stroke, myelopathy, and peripheral neuropathy should be recorded. A quantification of global cognitive functioning is also recommended, using, for example, the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).



In addition, among the neuropsychiatric disorders, it is important to collect information about depression symptoms because they can lead to gait instability and falls. The four-item Geriatric Depression Scale should be used as a screening test. A measure of anxiety is also proposed using the five-item Geriatric Anxiety Inventory.

Information on major orthopedic diagnoses (e.g., osteoarthritis), involving the cervical or lumbar vertebrae, pelvis or lower extremities, coded yes versus no, as well as the use of a walking aid, should also be recorded.

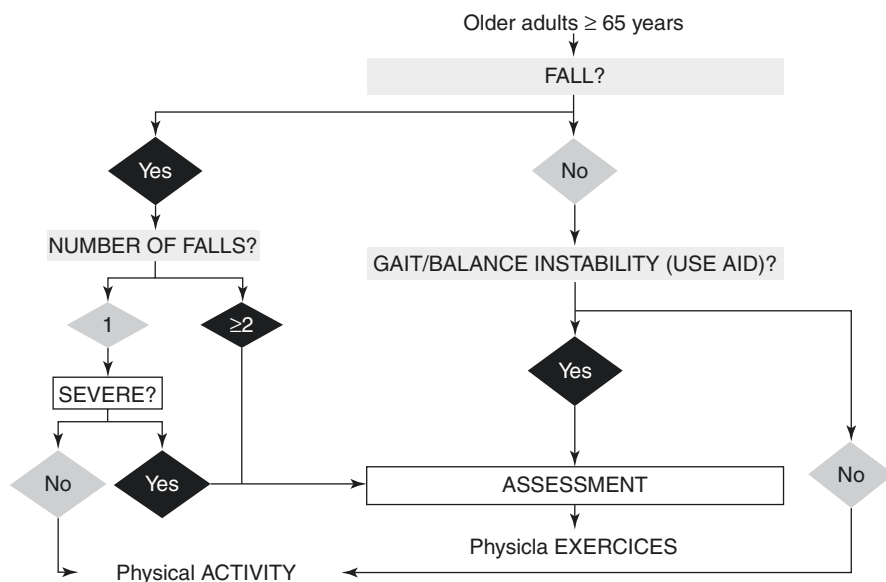
Information on sensory and motor subsystems such as muscle strength, lower-limb proprioception, and vision are required because the age-related impairment in the performance of these subsystems may affect gait performance.

It is important to assess the severity of falls. The severity of falls is related to several components that may be classified into four categories including fall-related injuries, the medical event which has caused the fall, the intensity of recurrent falls, and the associated comorbid conditions. The fall-related injuries which classify a fall as severe are (1) a moderate or a severe physical trauma including fractures, dislocations, voluminous intracranial or peripheral hematomas, trauma of the face, and cutaneous lacerations of significant size and/or deeper than the hypodermis; (2) the inability to stand up from the ground associated with resting on the ground for more than 1 hour and its potential consequences including rhabdomyolysis, hypothermia, bedsores, aspiration pneumonia, and dehydration; and (3) a post-fall syndrome, a functional complication of fall due to a partial or full motor, psychological, and/or cognitive incapacity, characterized by extrapyramidal rigidity, retropulsion, and standing phobia (stasisphobia). The signs of severity of fall may also be related to an acute medical event producing the fall such as cardiac rhythm or conduction disorders, strokes, heart failure, myocardial infarction, infectious diseases, and hypoglycemia in diabetic patients. As an example, syncopal loss of consciousness invariably leads to loss of postural tone and, when occurring in the upright position, leads to falls. Syncope should be considered as a severity criterion for falls due to fall-related injuries and the underlying cardiovascular etiology. Frequency of recurrent falls is also associated with fall severity. A recent increase in the number of falls should be considered as a marker of severity. Associated comorbid conditions, which make a relatively mild fall potentially dangerous because of fall-related consequences, should be systematically identified and a mild fall in the presence of comorbid conditions should be considered severe. Comorbid conditions related to fall severity are three or more fall risk factors, including balance and/or gait disorders validated with abnormal one-leg balance  $\leq 5$  seconds and a Timed Up and Go score  $\geq 20$  seconds, osteoporosis defined by a T score  $< 2.5$  SD on densitometry and/or a history of osteoporotic fracture, the use of anticoagulants, and social and/or familial isolation and/or living alone.

The role of laboratory testing and diagnostic evaluation for gait and balance disorders has not been well studied. Cerebral imaging in the absence of specific indication based upon clinical examination may not be necessary.

An algorithm to guide fall assessment is shown in Fig. 6.3. Caution is advised however, as recent evidence suggests that a fall assessment may always be needed in older adults, as up 30% of individuals with no history of falls still experience a fall. Table 6.5 shows the management (diagnosis, assessment, and treatment) of falls.





**Fig. 6.3** Algorithm proposing the management of falls

**Table 6.5** Management (diagnosis, assessment, and treatment) of falls

Questions	Criteria	Definitions
How to define fall?	Fall	Event that results in a person coming to rest inadvertently on the ground or floor or other lower level
	Recurrent fall	At least two falls in a 12-month period
How to identify severe falls?	Fall-related injuries	Moderate or severe physical traumas (fractures, dislocations, intracranial or voluminous peripheral hematomas, traumas of the face, and cutaneous lacerations of significant size and/or deeper than the hypodermis) Inability to stand up from the ground associated with resting on the ground for more than 1 hour and its potential consequences (rhabdomyolysis, hypothermia $\leq 35^{\circ}\text{C}$ , bedsores, aspiration pneumopathy, and dehydration) Post-fall syndrome: motor, psychological, and/or cognitive incapacity characterized by extrapyramidal rigidity, retropulsion, and stasiphobia
	Fall-related medical events	Cardiac rhythm or conduction disorders, strokes, heart failure, myocardial infarction, infectious diseases, and hypoglycemia in diabetic patients
	Fall-related comorbid conditions	Recent increase in the number of falls Number of risk factors for falls $\geq 3$ Balance and/or gait disorders (one-leg balance $\leq 5$ seconds and Timed Up and Go score $\geq 20$ seconds) Osteoporosis defined by a T score $< 2.5$ SD on osteodensitometry and/or a history of osteoporotic fracture Use of anticoagulants Social and/or familial isolation and/or living alone

(continued)

**Table 6.5** (continued)

Questions	Criteria	Definitions
How to assess falls?	Predisposing risk factors of falls	<p>Age <math>\geq 80</math></p> <p>Female gender</p> <p>A history of traumatic fractures</p> <p><math>\geq 5</math> drugs taken per day</p> <p>Psychoactive drugs (benzodiazepines, hypnotics, antidepressants, and neuroleptics)</p> <p>Cardiovascular drugs (diuretics, digoxin, or class I antiarrhythmic)</p> <p>Gait and/or balance disorders (one-leg balance <math>\leq 5</math> seconds and Timed Up and Go score <math>\geq 20</math> seconds)</p> <p>Low strength and/or muscular power of the lower limbs (body mass index <math>&lt; 21 \text{ kg/m}^2</math> or a weight loss <math>\geq 5\%</math> over 1 month or <math>\geq 10\%</math> over 6 months)</p> <p>Osteoarthritis of the lower limbs and/or of the spine</p> <p>Anomalies of the feet (toe deformation and severe callosity)</p> <p>Sensor disorders in the lower limbs</p> <p>Low visual acuity: assess visual acuity using the Monnoyer and/or Parinaud test charts</p> <p>Depressive syndrome: 4-item Geriatric dDepression sScale <math>\geq 1</math></p> <p>Cognitive decline: Mini- Mental Status of Folstein (MMSE) <math>&lt; 25</math> or MoCA <math>&lt; 26</math></p>
	Precipitating risk factors of falls	<p>Cardiovascular symptoms: dizziness, syncope, orthostatic hypotension</p> <p>Neurological symptoms: sensory-motor neurological deficiency</p> <p>Vestibular symptoms: vertigo, lateral deviation during Romberg test</p> <p>Metabolic disorders: hyponatremia, hypoglycemia, and hypoglycemic medication intake</p> <p>Environmental: examine lighting, cluttering, and the organization of the place the subject lives in as well as the shoes</p>
How to treat falls?	Systematic intervention when applicable	<p>Revision of the drugs while the subject takes psychoactive and cardiovascular drugs and/or the number of drugs is <math>\geq 4</math></p> <p>Correction of modifiable predisposing or precipitating factors</p> <p>Wearing of shoes with broad, low heels (2–3 cm) and firm, thin soles</p> <p>Regular practice of walking and/or any other physical activity that involves lower limb training and/or balance training</p> <p>Use of an adapted walking aid</p> <p>Vitamin D supplementation (at least 800 IU/day).</p> <p>Anti-osteoporotic treatment when indicated</p> <p>Education of recurrent fallers and their caregivers</p>
	Gait and/or balance disorders	<p>Performance of static and dynamic postural exercise</p> <p>Increase the strength and muscular power of the lower limbs</p> <p>Regular practice: 2 to 3 times per week</p> <p>Intensity of exercises: low to moderate</p>

## Conclusions

Falls represent an important medical problem in older adults, particularly in the cognitively impaired, given the amount of burden and disability that they generate. A systematic approach based on clinical assessment and performance-based measurements or using simple gait assessment can detect those at higher risk. We believe that cognitive assessment specifically focusing on domains such as executive function, attention, dual-task capabilities, and memory can help to optimally understand risk of falling [9]. In individual without history of falls, evidence supports the implementation of gait, and balance assessments yields key information for falls risk stratification. Dual-task gait can help to assess the motor-cognitive interface and may detect risk of falls in those with normal balance and single gait speed testing. There is not strong evidence that the remaining medical domains (orthostatic hypotension, visual impairment, medication review, activities of daily living, and cognitive impairment) should be screened in older adults without history of falls if the only purpose is to determine risk of falling. These domains were less frequently, or not at all, independently associated with falls in comprehensive longitudinal studies in those without history of falls [1, 2]. If the individual has previous history of falls, a comprehensive evaluation is needed as described in Table 6.2. Certain specific cognitive aspects including attention and executive function need to be part of the fall risk evaluation in addition to identification of global cognitive impairment, mild cognitive impairment, and/or dementia syndromes.

**Acknowledgments** We are indebted to Dr. Yanina Sarquis-Adamson, from the “Gait and Brain Lab,” Division of Geriatric Medicine at St. Joseph’s Health Care, London, ON, Canada, for her endless assistance in the preparation of this chapter.

---

## References

1. Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. *J Am Geriatr Soc.* 2005;53(12):2190–4.
2. Ganz DA, Bao Y, Shekelle PG, Rubenstein LZ. Will my patient fall? *JAMA.* 2007;297(1):77–86.
3. Isaacs B. The Giants of geriatrics. In: *The challenge of geriatric medicine.* Oxford: Oxford University Press; 1992. p. 1–7.
4. Beauchet O, Dubost V, Revel Delhom C, et al. How to manage recurrent falls in clinical practice: guidelines of the French Society of Geriatrics and Gerontology. *J Nutr Health Aging.* 2011;15(1):79–84.
5. WHO global report on falls prevention in older age. 2007.; [https://www.who.int/ageing/publications/Falls\\_prevention7March.pdf](https://www.who.int/ageing/publications/Falls_prevention7March.pdf).
6. Muir SW, Beauchet O, Montero-Odasso M, Annweiler C, Fantino B, Speechley M. Association of executive function impairment, history of falls and physical performance in older adults: a cross-sectional population-based study in eastern France. *J Nutr Health Aging.* 2013;17(8):661–5.
7. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. *Mov Disord.* 2013;28(11):1520–33.
8. Taylor ME, Lord SR, Delbaere K, Mikolaizak AS, Close JC. Physiological fall risk factors in cognitively impaired older people: a one-year prospective study. *Dement Geriatr Cogn Disord.* 2012;34(3–4):181–9.

9. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: implications for risk assessment and prevention. *J Am Geriatr Soc.* 2018;66(2):367–75.
10. Montero-Odasso M, Hogan DB. Falls & fall-related injuries Special Interest Group: a call to action. *Can Geriatr J.* 2016;19(4):202–3.
11. Montero-Odasso M. Falls as a geriatric syndrome: how to prevent them? how to treat them? In: Duque G, Kiel D, editors. *Osteoporosis in older persons*. London: Springer; 2009. p. 110–25.
12. Vlaeyen E, Stas J, Leysens G, et al. Implementation of fall prevention in residential care facilities: a systematic review of barriers and facilitators. *Int J Nurs Stud.* 2017;70:110–21.
13. Cohen D, Morrison A. Interventions for preventing falls among older adults living in the community. *Am Fam Physician.* 2017;95(3):152–3.
14. Khow KSF, Visvanathan R. Falls in the aging population. *Clin Geriatr Med.* 2017;33(3):357–68.
15. Oliver D, Daly F, Martin FC, McMurdo ME. Risk factors and risk assessment tools for falls in hospital in-patients: a systematic review. *Age Ageing.* 2004;33(2):122–30.
16. Howcroft J, Kofman J, Lemaire ED. Review of fall risk assessment in geriatric populations using inertial sensors. *J Neuroeng Rehabil.* 2013;10(1):91.
17. Gates S, Smith LA, Fisher JD, Lamb SE. Systematic review of accuracy of screening instruments for predicting fall risk among independently living older adults. *J Rehabil Res Dev.* 2008;45(8):1105–16.
18. Rubenstein LZ, Robbins AS, Josephson KR, Schulman BL, Osterweil D. The value of assessing falls in an elderly population. A randomized clinical trial. *Ann Intern Med.* 1990;113(4):308–16.
19. Tinetti ME. Where is the vision for fall prevention? *J Am Geriatr Soc.* 2001;49(5):676–7.
20. Bloem BR, Boers I, Cramer M, Westendorp RG, Gerschlager W. Falls in the elderly. I. Identification of risk factors. *Wien Klin Wochenschr.* 2001;113(10):352–62.
21. Campbell AJ, Borrie MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. *J Gerontol.* 1989;44(4):M112–7.
22. Tinetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury during falls by older persons in the community. *J Am Geriatr Soc.* 1995;43(11):1214–21.
23. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* 2001;49(5):664–72.
24. Lach HW, Reed AT, Arfken CL, et al. Falls in the elderly: reliability of a classification system. *J Am Geriatr Soc.* 1991;39(2):197–202.
25. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* 1988;319(26):1701–7.
26. Tinetti ME, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT trial? Frailty and injuries cooperative studies of intervention techniques. *Am J Epidemiol.* 1996;144(4):389–99.
27. Agostini JV, Tinetti ME. Drugs and falls: rethinking the approach to medication risk in older adults. *J Am Geriatr Soc.* 2002;50(10):1744–5.
28. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc.* 1999;47(1):30–9.
29. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* 1999;47(1):40–50.
30. Isaacs B. Clinical and laboratory studies of falls in old people. Prospects for prevention. *Clin Geriatr Med.* 1985;1(3):513–24.
31. Whitney J, Close JC, Jackson SH, Lord SR. Understanding risk of falls in people with cognitive impairment living in residential care. *J Am Med Dir Assoc.* 2012;13(6):535–40.
32. Kearney FC, Harwood RH, Gladman JR, Lincoln N, Masud T. The relationship between executive function and falls and gait abnormalities in older adults: a systematic review. *Dement Geriatr Cogn Disord.* 2013;36(1–2):20–35.
33. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing.* 2012;41(3):299–308.
34. Scherder E, Eggermont L, Swaab D, et al. Gait in ageing and associated dementias; its relationship with cognition. *Neurosci Biobehav Rev.* 2007;31(4):485–97.

35. Beauchet O, Annweiler C, Callisaya ML, et al. Poor gait performance and prediction of dementia: results from a meta-analysis. *J Am Med Dir Assoc*. 2016;17(6):482–90.
36. Beauchet O, Annweiler C, Dubost V, et al. Stops walking when talking: a predictor of falls in older adults? *Eur J Neurol*. 2009;16(7):786–95.
37. Canada ASo. A new way of looking at the impact of dementia in Canada. 2012; <https://alzheimer.ca/en/cornwall/Awareness/A-new-way-of-looking-at-dementia>.
38. Canada PHAo. Seniors' Falls in Canada. 2014; Second Report: [http://www.phac-aspc.gc.ca/seniors-aines/publications/public/injury-blessure/seniors\\_falls-chutes\\_aines/assets/pdf/seniors\\_falls-chutes\\_aines-eng.pdf](http://www.phac-aspc.gc.ca/seniors-aines/publications/public/injury-blessure/seniors_falls-chutes_aines/assets/pdf/seniors_falls-chutes_aines-eng.pdf).
39. Morgan D, Funk M, Crossley M, Basran J, Kirk A, Bello-Haas V. The potential of gait analysis to contribute to differential diagnosis of early stage dementia: current research and future directions. *Can J Aging*. 2007;26(1):19–32.
40. van Iersel MB, Benraad CE, Rikkert MG. Validity and reliability of quantitative gait analysis in geriatric patients with and without dementia. *J Am Geriatr Soc*. 2007;55(4):632–4.
41. van Iersel MB, Hoefsloot W, Munneke M, Bloem BR, Olde Rikkert MG. Systematic review of quantitative clinical gait analysis in patients with dementia. *Z Gerontol Geriatr*. 2004;37(1):27–32.
42. Allan LM, Ballard CG, Burn DJ, Kenny RA. Prevalence and severity of gait disorders in Alzheimer's and non-Alzheimer's dementias. *J Am Geriatr Soc*. 2005;53(10):1681–7.
43. Merory JR, Wittwer JE, Rowe CC, Webster KE. Quantitative gait analysis in patients with dementia with Lewy bodies and Alzheimer's disease. *Gait Posture*. 2007;26(3):414–9.
44. Alexander NB. Gait disorders in older adults. *J Am Geriatr Soc*. 1996;44(4):434–51.
45. Goldman WP, Baty JD, Buckles VD, Sahrman S, Morris JC. Motor dysfunction in mildly demented AD individuals without extrapyramidal signs. *Neurology*. 1999;53(5):956–62.
46. Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. *J Am Geriatr Soc*. 2003;51(11):1633–7.
47. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. *J Neurol Neurosurg Psychiatry*. 2007;78(9):929–35.
48. Webster KE, Merory JR, Wittwer JE. Gait variability in community dwelling adults with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006;20(1):37–40.
49. Beauchet O, Dubost V, Herrmann FR, Kressig RW. Stride-to-stride variability while backward counting among healthy young adults. *J Neuroeng Rehabil*. 2005;2:26.
50. Hausdorff JM, Yogev G, Springer S, Simon ES, Giladi N. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res*. 2005;164(4):541–8.
51. Allali G, Kressig RW, Assal F, Herrmann FR, Dubost V, Beauchet O. Changes in gait while backward counting in demented older adults with frontal lobe dysfunction. *Gait Posture*. 2007;26(4):572–6.
52. Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. *Neurology*. 1993;43(2):268–79.
53. Dubost V, Annweiler C, Aminian K, Najafi B, Herrmann FR, Beauchet O. Stride-to-stride variability while enumerating animal names among healthy young adults: result of stride velocity or effect of attention-demanding task? *Gait Posture*. 2008;27(1):138–43.
54. Dubost V, Kressig RW, Gonthier R, et al. Relationships between dual-task related changes in stride velocity and stride time variability in healthy older adults. *Hum Mov Sci*. 2006;25(3):372–82.
55. Abernethy B. Dual-task methodology and motor skills research: some applications and methodological constraints. *J Hum Mov Stud*. 1988;14(3):31.
56. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. *Lancet*. 1997;349(9052):617.
57. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60(11):2127–36.
58. Bloem BR, Gussekloo J, Lagaay AM, Remarque EJ, Haan J, Westendorp RG. Idiopathic senile gait disorders are signs of subclinical disease. *J Am Geriatr Soc*. 2000;48(9):1098–101.

59. Sudarsky L. Geriatrics: gait disorders in the elderly. *N Engl J Med*. 1990;322(20):1441–6.
60. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997;337(10):670–6.
61. Dhese JK, Jackson SH, Bearne LM, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. *Age Ageing*. 2004;33(6):589–95.
62. Montero-Odasso M, Schapira M, Varela C, et al. Gait velocity in senior people. An easy test for detecting mobility impairment in community elderly. *J Nutr Health Aging*. 2004;8(5):340–3.
63. Dubost V, Beauchet O, Manckoundia P, Herrmann F, Mourey F. Decreased trunk angular displacement during sitting down: an early feature of aging. *Phys Ther*. 2005;85(5):404–12.
64. Hsiao-Wecksler ET, Katdare K, Matson J, Liu W, Lipsitz LA, Collins JJ. Predicting the dynamic postural control response from quiet-stance behavior in elderly adults. *J Biomech*. 2003;36(9):1327–33.
65. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2004;52(7):1121–9.
66. Bloem BR, Haan J, Lagaay AM, van Beek W, Wintzen AR, Roos RA. Investigation of gait in elderly subjects over 88 years of age. *J Geriatr Psychiatry Neurol*. 1992;5(2):78–84.
67. Woo J, Ho SC, Yu AL. Walking speed and stride length predicts 36 months dependency, mortality, and institutionalization in Chinese aged 70 and older. *J Am Geriatr Soc*. 1999;47(10):1257–60.
68. Carey BJ, Potter JF. Cardiovascular causes of falls. *Age Ageing*. 2001;30(Suppl 4):19–24.
69. Lipsitz LA. Orthostatic hypotension in the elderly. *N Engl J Med*. 1989;321(14):952–7.
70. Montero-Odasso M, Schapira M, Duque G, Soriano ER, Kaplan R, Camera LA. Gait disorders are associated with non-cardiovascular falls in elderly people: a preliminary study. *BMC Geriatr*. 2005;5:15.
71. Yamada M, Aoyama T, Arai H, et al. Dual-task walk is a reliable predictor of falls in robust elderly adults. *J Am Geriatr Soc*. 2011;59(1):163–4.
72. Muir SW, Speechley M, Borrie M, Montero Odasso M. Fall risk in cognitively impaired older adults: the value of gait assessment under dual task test challenges. *Can J Geriatr*. 2010;13(1):46.
73. Montero Odasso M. Falls as a geriatric syndrome: mechanisms and risk identification. In: Duque G, Kiel DP, editors. *Osteoporosis in older persons*. Oxford: Springer International Publishing; 2015. p. 171–86.



# Gait Variability and Fall Risk in Older Adults: The Role of Cognitive Function

# 7

Frederico Pieruccini-Faria, Manuel Montero-Odasso,  
and Jeffrey M. Hausdorff

## Gait Variability and Normal Aging

### Gait Variability as an Index of Walking Performance

Human gait is a complex motor skill characterized by sequential footfalls rhythmically generated by the central nervous system and adjusted by sensory feedback allowing safe navigation on different terrains [1]. Measurements of distance and durations between footfalls can be used to estimate an individual's gait performance (Fig. 7.1). Fluctuation in time and distance, from one footfall to the

---

F. Pieruccini-Faria (✉)

Department of Medicine, Division of Geriatric Medicine, University of Western Ontario,  
London, ON, Canada

Gait and Brain Lab, Parkwood Institute and Lawson Health Research Institute,  
London, ON, Canada

e-mail: [fpierucc@uwo.ca](mailto:fpierucc@uwo.ca); [Frederico.Faria@sjhc.london.on.ca](mailto:Frederico.Faria@sjhc.london.on.ca)

M. Montero-Odasso

Departments of Medicine (Geriatric Medicine), and Epidemiology and Biostatistics,  
Schulich School of Medicine & Dentistry, University of Western Ontario,  
London, ON, Canada

Gait and Brain Lab, Parkwood Institute, Lawson Health Research Institute,  
London, ON, Canada

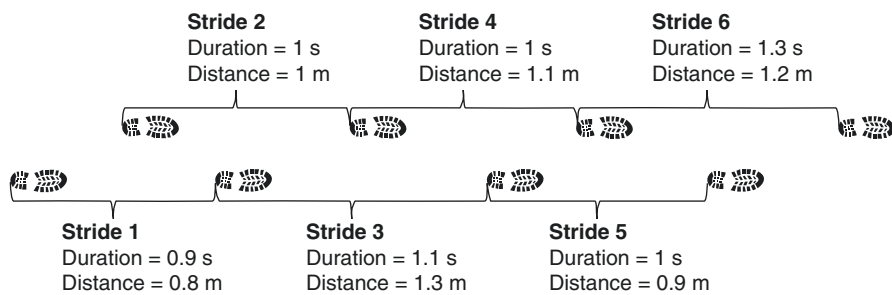
J. M. Hausdorff

Center for the Study of Movement, Cognition and Mobility, Neurological Institute,  
Tel Aviv Medical Center, Tel Aviv, Israel

Department of Physical Therapy, Sackler Faculty of Medicine and Sagol School of  
Neuroscience, Tel Aviv University, Tel Aviv, Israel

Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery, Rush University  
Medical Center, Chicago, IL, USA

e-mail: [jhausdor@tlvmc.gov.il](mailto:jhausdor@tlvmc.gov.il)



$$\text{Stride time variability as CV} = \left( \frac{\text{SD of durations (Strides 1 to 6)}}{\text{Mean durations (Strides 1 to 6)}} \right) \times 100 = \mathbf{13.1\%}$$

$$\text{Stride length variability as CV} = \left( \frac{\text{SD of distances (Strides 1 to 6)}}{\text{Mean distances (Strides 1 to 6)}} \right) \times 100 = \mathbf{17.8\%}$$

**Fig. 7.1** In this example, six subsequent strides from the left and right legs, defined by curly brackets, are quantified using heels' footprints as references for measurements of duration and distance between footfalls in the persons' sagittal plane. In a more simplified manner, studies have also calculated the CV from subsequent strides based on just one leg (e.g., strides 1, 3, and 5 or strides 2, 4, and 6). Variability extraction can be estimated using CV calculation (shaded areas)

next, is referred to as step-to-step variability. Researchers have measured *gait variability* using a variety of parameters. These include, for example, step/stride length (distance between subsequent footfalls in the sagittal plane), step/stride width (distance between subsequent footfalls in the frontal plane), step/stride time (time spent from one footfall to the next), double support time (time spent with both feet touching the floor), stance time (time spent with one foot touching the floor), swing time (time spent with one foot not touching the floor), and foot clearance (minimum foot-floor distance while swinging before its respective contact with the floor).

The magnitude of the spatial and temporal variability of gait parameters can be useful for assessing motor control mechanisms. For example, the timing of the fluctuations between footfalls may provide more detailed information about the neural control of rhythmicity (internal "clock") than just the mean duration, because the latter does not provide information about variations from one step to the next over a recording period. Because gait patterns result from interactions among different organic sub-systems including sensory, musculoskeletal, cardiac, cognitive, and affective domains, impairment in one or more physiologic domains may negatively affect voluntary stepping generation and step-to-step variability (see Fig. 7.1). Notably, aging and disease have a known negative impact on many of these sub-systems. Thus, measuring gait variability can be



useful not only to understand the dynamics of gait control but also to monitor and predict functional decline.

## Quantifying Gait Variability

Gait variability can only be accurately measured with electronic equipment specially developed to record the distance and/or duration between each footfall. Several different methodologies have been applied to assess gait variability including footswitches [2], accelerometers [3], electronic mats embedded with pressure sensors [4], infrared systems [5], and video cameras [6]. Stride-to-stride fluctuations can be analyzed in many different ways. Some measures examine the changes over time (or space), i.e., gait dynamics. These can be determined, for example, using metrics based on entropy [7], detrended fluctuation analysis [8], Lyapunov exponent [9], or the fractal index [10]. Many of these approaches assume relatively long measurements of gait to quantify the randomness (i.e., chaos) in the data set recorded from an individual's behavior. Thus, in clinical research, where that assumption often may not be achieved, the magnitude of the stride-to-stride fluctuation may be calculated instead. This can be done using several approaches including spectral analyses and root-mean-square analyses or by calculating the standard deviation (SD) of a gait parameter, for example. One of the most common approaches used in clinical research is to evaluate the coefficient of variation (CV) [11, 12]. The CV is calculated by dividing the SD of steps or strides by its mean times hundred; thus, this variability parameter is expressed as a percentage (Fig. 7.1). This approach removes the influence of absolute gait characteristics (i.e., mean) from the variance of steps. Therefore, this approach facilitates the comparison of the magnitude of variability across different populations (e.g., patients vs. healthy controls) whose mean values may differ. Using this approach, the gait measurement should capture at least 12 steps to achieve a minimal level of test-to-test reliability of gait variability [6]; for increased or maximum test-to-test reliability, more than 50 steps may be necessary [13]. Another concern regarding reliability in variability analysis is the influence of self-select gait speed on gait dynamics since people may present different preferred gait speeds. However, a study in community-dwelling older adults demonstrated no meaningful interference of voluntary increase in gait speed over step length variability [14], although a substantial increase in step width variability was observed. In order to account for this potential confounder, some studies have adjusted the variability analysis for gait speed [15, 16]. Variability has been considered an important measure of gait stability, in part because it is cross-sectional and prospectively associated with falls. In this chapter, we will present evidence showing that increased gait variability can be a marker of high risk of falling in normal aging and, particularly, in older adults with neurological and neurodegenerative disorders. Although inconsistencies in the specifics of the protocols and the results reported in the literature exist, many studies have pointed toward aging as an important cause of increased gait variability in older people.

## Gait Variability and Aging

Low variability is commonly observed in over-learned, as compared to recently learned, movements and motor tasks [17, 18]. In other words, low variability can be an estimate of an individual's motor proficiency [17] or the automaticity of a motor task. As for simplicity, automaticity can be defined as the amount of conscious effort (i.e., attention) necessary to perform a given motor task. Hausdorff et al. [19] demonstrated that step time variability decreases as children become older, over a range of 4–15 years of age, after which it reaches a plateau. A more recent study [20] demonstrated that changes in gait variability occurring from childhood to adulthood happen independently of changes in absolute values of step/stride time, length, and width that can be strongly influenced by body dimensions and mass distribution. Therefore, this reduction in gait variability that accompanies the maturation process resembles the initial motor learning stages in which individuals pay more attention to the motor task to guarantee accurate execution [21]. It is also argued that changes in variability during childhood are associated with physiological, structural, and psychological development [22, 23]. These physiologic changes may lead to the discovery and subsequent learning of a biomechanically efficient gait pattern by the central nervous system [1], consequently reducing gait variability at the end of the maturation process.

Previous research has shown that after the sixth decade of life, gait variability substantially increases again [10, 24, 25], a kind of mirror image of the maturation process. Normative data have demonstrated a gradual but significant increase from 70 to 85 years of age confirming the impact of the aging process on the increase of spatial and temporal gait variability parameters [26, 27]. This increase in gait variability in elderly individuals ( $\geq 65$  years of age) has been also associated with the presence of comorbidities and functional decline [28]. Age-associated physiologic changes including muscle weakness (e.g., sarcopenia), degenerative joint disease (e.g., osteoarthritis), vision impairment (e.g., cataracts, low contrast sensitivity), reduced proprioceptive sensitivity, and cognitive impairments (e.g., poor memory and attention) negatively impact an individual's mobility (recall Fig. 7.2), ultimately resulting in loss of independence [29–31].

## Gait Variability and Falls

A fall is defined as an “unintentional coming to floor, ground or other lower level surface not due to seizure or stroke” [32], as described in Chap. 1. Falls place enormous health and financial burden on aged societies since one-third of older adults will suffer at least one fall within 12 months [33]. It is estimated that medical costs attributed to fatal and non-fatal falls are 50 billion dollars just in the United States [34]. Importantly, accidental falls are one of the most common causes of hospitalizations due to fractures [35–37] and head injuries [38] in individuals over 65 years of age [39]. Therefore, understanding the causes of gait control disturbances is crucial to prevent falls since nearly 40% of such falls happen while walking [40].



with increased stride time variability in older adults with dementia [44]. These results reinforce the notion that increased stride-to-stride fluctuations represent stability problems in older adults and not just impaired rhythmicity (impaired “internal clock”).

Another important finding is that attention may modulate both body stability and gait variability in older adults. Studies have used protocols in which individuals are asked to walk while performing a concurrent cognitive task (i.e., dual-task) to understand the impact of cognitive processing on stability measures during gait. One study demonstrated that older adults who had larger increase in gait variability while performing a dual-task, compared with single-task gait performance (i.e., high dual-task cost) also had an increased risk to suffer a fall in the next 12-month follow-up period, compared with those with reduced variability when dual tasking [45]. This suggests that cognitive difficulties may have an important influence on an individual’s stability which may be reflected in increased gait variability performance.

## **Gait Variability and Fear of Falling**

Fear of falling (FoF) is a strong predictor of falls because it reveals lack of balance confidence [32] since individuals with FoF often report to avoid activities that may expose them to a new fall episode. FoF and high temporal stride-to-stride variability can be found in individuals with unspecific gait and balance impairments, not caused by neurodegenerative or other identifiable processes [46]. Although FoF and stride variability are associated, the cause-effect mechanisms linking these behaviors remain unknown. One possibility is that if FoF is sufficiently severe, then each step becomes effortful and demanding, disturbing the smoothness and automaticity of the gait pattern; however, this is currently just speculation.

A significant relationship, although of low magnitude, between gait variability and FoF in older adults was confirmed by a meta-analysis [47]. Further, studies reviewed by this meta-analysis identified that individuals with FoF frequently walk with increased gait variability in all parameters (i.e., time and distance). Consistent with previous studies, FoF may be considered as a cortical level dysfunction that impacts gait control [46, 48]. The impact of FoF, at the cortical level, is suggested by evidence showing that individuals with FoF may present affective dysfunction including increased neuroticism and depression, which are both associated with poor balance stability and falls in older people [49]. Although affective dysfunction and cognitive problems may co-exist in older adults, a recent study demonstrated that affective dysfunction may cause balance disturbances independently of participants’ cognitive performance [50]. FoF is also associated with unspecific brain lesions from concussions that globally affects cognitive processing including attention and executive functions [46, 51]. In summary, FoF and gait variability may progress in parallel as people age and are both useful biomarkers of mobility decline, the risk of falls, and neurological integrity.

## **Gait Variability, Sex, and Falls**

The influence of sex on gait variability has been understudied. A recent study with a sample of 1390 non-demented older adults found that women have higher step/stride duration, length, and width variabilities compared with men [52]. In addition, this study showed that the percentage increase in gait variability during multi-tasking was a predictor of falls in women, but not in men. The increase in gait variability when multi-tasking in women (15–35%) was higher than in men, for all gait parameters. This suggests that, compared with men, women may be at higher risk of falling in contexts of increased cognitive “stress” (e.g., walking and talking). Still, others have reported that the predictive value of dual-task gait variability persists even when controlling for sex [53]. These discrepancies in the literature may suggest that, perhaps, uncontrolled socioeconomic aspects [54] could be causing such differences in gait performance between sexes. Thus, studies should take into consideration sex as a potential covariate in statistical analysis when comparisons between experimental groups are performed, particularly when sex distribution between groups is unequal.

## **Gait Variability, Obstacle Negotiation, and Falls**

Obstacles in the pathway are one of the most common fall triggers among older adults [40, 55]. Observational studies identified that difficulties adjusting balance control to safely avoid obstacle collisions represent nearly 40% of all falls suffered by older adults [40]. Experimental studies have provided empirical evidence of abnormal preparatory balance adjustments [56] and higher spatial and temporal gait variability [57] in older individuals at higher risk of falling compared with low-risk individuals. This subtle increase in gait variability in high-risk individuals occurs within the last few steps preceding an obstacle avoidance, where foot-to-obstacle distance adjustments are necessary to avoid a collision. It is argued that higher-order central processing deficits, including action planning, could contribute to obstacle negotiation abnormalities [58] since these resources are crucial to adjust diverse human behaviors [59]. Furthermore, the fear of suffering a new fall while navigating surrounded by postural threats cannot be discarded since it has been associated with balance problems and higher gait variability in older adults [41, 60]. The mechanisms of altered obstacle negotiation performance and their predictive validity of incidental falls are yet to be determined.

---

## **Gait Variability and Clinical Conditions and Falls**

### **Cardiovascular Conditions**

Cardiovascular problems, including congestive heart failure, myocardial infarction, atrial fibrillation, and peripheral arterial disease, have been associated with falls without an apparent cause [61–64]. It is argued that failure to supply blood to both

muscles and brain when transitioning between postures (e.g., sit to stand) can cause such falls [65] (Fig. 7.2). For example, insufficient blood supply to the brain, as a result of orthostatic hypotension, could lead individuals to lose consciousness and then faint, whereas low blood supply to muscles would weaken posture reactions to compensate for instabilities while walking [64]. Moreover, the insufficient blood supply in leg muscles could cause fatigue, a condition that increases gait variability [66], therefore predisposing individuals to a subtle loss of balance while navigating. Hausdorff et al. [67] demonstrated that older adults with severe cardiac problems, particularly congestive heart failure, have higher gait variability compared with older adults with normal cardiac functioning. They suggested that reduced blood supply to muscles, as a result of an inefficient cardiovascular system, could be the main cause for increased gait unsteadiness in these individuals.

## Poststroke

Stroke survivors often exhibit motor sequelae resulting from lack of blood supply in motor neurons when a brain hemorrhage occurs. Hence, gait performance can be markedly affected by a stroke. Stroke survivors often exhibit notable asymmetry between steps since the majority of stroke events occur unilaterally. Spatial and temporal variability poststroke is higher compared with normal reference values, although individuals with different stroke severities surprisingly presented comparable gait variabilities [68, 69]. It was also shown that both spatial and temporal gait variability significantly improved approximately 45 days after the stroke episode, independently of cognitive load conditions (i.e., single or dual-task) in which gait performance was assessed [70, 71]. Interestingly, although stroke survivors may experience balance difficulties due to sensory and motor impairments caused by vascular lesions in the brain, no changes in the variability of the base of support (step width variability) were found after patient discharge. These results suggest that changes in gait variability potentially reflect ongoing neuronal plasticity in the brain, rather than balance impairments, during the recovery process. It is important to highlight that there is a very high inter-subject variability in poststroke populations, and for this reason, future studies should aim to determine whether the locus where a stroke occurred had a specific impact on gait variability performance and recovery.

## Peripheral Neuropathy

Although centrally generated, gait control needs to be constantly adjusted by sensory information. Receptors in muscles, joints, and skin provide real-time information about the current state of lower limbs relative to each other and the surface while walking. This information is then used by the central nervous system in a more controlled or reflexive manner to adjust steps so that stability can be maintained. These adjustments become even more important in challenging situations

where the walking surface is less predictable (e.g., rocky ground). A sequence of experiments have empirically demonstrated the concepts aforementioned by evaluating gait performance of individuals diagnosed with peripheral neuropathy tested on an irregular surface covered with prism-shaped pieces in a room with lights dimmed [72–75]. These experiments showed the importance of proprioceptive information from the lower limbs to regulate temporal and spatial gait parameters. Notably, when comparing neuropathic individuals with and without a history of recent falls [76], differences were only seen when participants of the study were tested in the experimental (irregular surface and dimmed lights) but not in the baseline gait condition. Moreover, although groups had comparable neuropathic scores, one group had higher gait variability and more falls than the other suggesting that an additional impairment, not measured by the study, could have played a role in walking performance differences. It is also possible that fallers with peripheral neuropathy had worse cognitive capabilities, therefore limiting their capacity to compensate for impaired sensory processing. This is plausible because attention can be used to adjust balance stability during situations of impoverished sensory information [77–79]. More studies are still needed to enhance our understanding regarding possible interactions among neuropathy, gait variability, and cognitive deficits in older adults.

## Depression

Depression in later life is common, reaching an average prevalence of 13.5% for all depression syndromes [80]. Although the association between depression and psychomotor slowness [49, 81, 82] and falls [83–85] has been relatively well established, few studies have investigated the role of depression on gait variability [86–88]. In young adults, depression can increase stride-to-stride time variability independently of depression subtype (e.g., unipolar or bipolar) [89]. A study found that the severity of depressive symptoms is associated with increased temporal variability in older adults although it is currently unknown its relationship with spatial variability [88]. Other studies have also demonstrated that poor executive function performance in older individuals with a clinical diagnosis of depression was associated with worse gait variability, but only when gait was assessed during dual-task conditions [87]. These studies suggest a potential interplay between depression and gait variability that may be mediated by executive function impairments (e.g., planning, set-shifting, and inhibition).

## Gait Variability, Executive and Memory Functions, and Falls

Executive functions are higher-order cognitive functions often associated with complex thinking and attention (e.g., planning and problem-solving). Low performance in executive functions, but not memory [90, 91], has been associated with high temporal [49] and spatial gait variabilities [91], as well as high risk of falls in



older populations with and without pre-existing balance impairments [93]. Recently, a meta-analysis demonstrated the existence of significant associations between intra-individual variability of executive function performance (i.e., reaction time variability) and falls in older adults [94], although an association between variability of executive functions performance and gait variability has not been established yet [95].

Another meta-analysis provided compelling evidence that the risk of falls with injuries (e.g., fractures) doubles in older adults with impaired executive function [96]. This could suggest that executive function contributes to protective responses that may reduce the intensity of the impact during a fall episode. Alternatively, the association may be more direct as every-day walking places a number of cognitive demands on safe ambulation (e.g., response inhibition, shared attention, planning, obstacle avoidance) since individuals with low executive function performance may not be able to effectively estimate environmental hazards [97–99]. From this perspective, executive functions could be important to better estimate the risks associated with certain situations with a great potential to cause serious injuries (e.g., falls with fractures) while navigating [98].

Notably, executive function abilities are linearly associated with increased stride time variability [92, 100]. This may explain why increased gait variability [101] and risk of falls [102, 103] are found in pre-dementia stages (i.e., mild cognitive impairment) when individuals may present decline in executive function performance, although still capable of performing activities of daily living independently [104]. Thus, it seems that not only is executive function associated with gait variability and fall risk, but specific disparate associations with cognitive performances may mediate the link between gait variability and falls.

While the association between executive functions and risk of falls in older adults has been explored in the literature, less is known about the association between memory and risk of falls. A previous study [105] conducted on a sample of individuals with mild cognitive impairment revealed that those with specific memory impairments had worse spatial (stride length) and temporal (swing time) variabilities compared with individuals with non-specific memory impairments. In a small cross-sectional study [106], variability was related to executive function, but not memory. A recent study conducted on 3426 cognitively normal older adults [107] found stronger cross-sectional and longitudinal associations between high temporal variability (swing time SD) at baseline and verbal episodic memory decline over a mean follow-up period of 1.9 years.

Other studies also demonstrated that short-term episodic memory performance can predict falls among older adults [108–110], although a more recent study in a relatively small cohort did not confirm this association when controlling for IQ (intellectual quotient) [111]. These discrepancies may be attributed to differences in sample size, study design, lack of adjustments for important confounders, and instrumentation used to assess memory performance across studies. An important aspect of these associations is whether cognitive domains mediate the association between gait variability and falls occurrence. Table 7.1 summarizes associations among gait variability, falls, and cognitive domains mentioned in this topic.



**Table 7.1** Matrix of associations between motor and cognitive impairments found in the literature. It is important to keep in mind that these relationships are complex as some view EF\_var as a form of EF and may not be considered an independent cognitive domain

Motor impairment	Cognitive domain			
	EF	Memory	EF_var	Memory_var
High temporal gait variability	Yes	Yes	No	NA
High spatial gait variability	Yes	No	No	NA
Falls	Yes	Yes	Yes	NA

*Note.* EF executive functions, EF\_var executive function variability (i.e., intra-individual reaction time variability), Memory\_var memory variability, NA not available. “Yes” denotes existing significant associations between motor and cognitive impairments as described in the literature

Gait Variability and Falls in Neurodegenerative Diseases

Neurodegenerative processes affecting both cortical [112] and subcortical [113] structures in the brain are consistently associated with high spatial and temporal gait variability. In addition to the cardinal disease symptoms, gait performance and mobility have been found to be profoundly affected by neurodegenerative diseases. The most prevalent neurodegenerative diseases among older adults are Alzheimer’s disease (AD) [114] and Parkinson’s disease (PD) [115]. Patients manifesting with these neurodegenerative diseases often have a slower gait speed and a higher risk of falls, compared to individuals at the same age and sex [116]. As the disease progresses, mobility problems become more evident and begin to limit activities of daily living [117]. Importantly, because of a rapidly aging of our society, the burden caused by these neurodegenerative diseases has also followed the population growth. Thus, identifying low-cost and reliable markers of ongoing pathology can be crucial to monitor the progression of neurodegenerative diseases.

Gait Variability and Falls in Mild Cognitive Impairment (MCI) and Alzheimer’s Disease (AD)

In addition to the cardinal AD symptoms (i.e., short-term memory and disorientation problems), individuals diagnosed with AD often have mobility problems, even in the early stages of the disease [118–120]. Patients in the initial AD stage may present with spatial and temporal stride variability ranging from 2.5% to 4% [117, 120], whereas in later disease stages, these values can reach up to 7–12% [117]. The coincident increase of gait variability and disease progression are demonstrated by recent studies that have shown the heightened risk of falls with injuries [103, 121] and gait variability [122] in MCI, considered a pre-dementia state, which reinforces the notion that variability is an early marker of ongoing neurodegenerative processes in the brain.

Importantly, the presence of frailty in older adults with and without dementias amplifies gait variability [123, 124]. Physical performance can be extremely deteriorated in AD due to physical inactivity that can be caused by several factors including lack of independence, apathy, depression, and malnutrition. Hence, it is

important to consider the influence of functional capacity when comparing gait variability performance, independently of cognitive capacity.

Stride length variability appears to be a sensitive marker of pre-dementia stages [125] and AD progression [117]. In addition, high stride time variability is associated with a history of falls in different subtypes of pre-dementia stages including individuals with non-amnesic and amnesic mild cognitive impairment [15]. Individuals with AD in later disease stages have higher variability compared with individuals in early stages [117]. Furthermore, stride length variability also distinguished AD patients with from those without a history of recent falls, irrespective of the disease stage. A study among 2496 individuals with different levels of cognitive decline and dementia subtypes found that higher stride time variability was associated with a history of falls in mild and in moderate non-AD dementia only [15]. Taken together, these studies suggest that stride length variability can be a sensitive gait parameter to predict both falls and AD progression, while stride time variability can be a sensitive marker of risk of falls and progression to non-AD dementia type.

## Frontal Temporal Dementia (FTD)

FTD is characterized by progressive deficits in behavior, executive function, and language. The disorder is the third most common form of dementia across all age groups, after Alzheimer's disease and dementia with Lewy bodies, and is a leading type of early-onset dementia [126]. Executive and language dysfunctions are both used in the FTD diagnosis and classification of its variants. Postural and gait problems, including slowness, postural instability, and axial rigidity, may also be present even in the early stages of the disease [127]. Motor signs may help differentiate FTD from other dementias particularly in early stages when typical cognitive deficits are still very mild. A study demonstrated remarkable differences in gait performance of individuals with AD and FTD behavioral variant. Stride time variability was significantly heightened in patients with FTD compared to AD and controls, and this association was not related to several confounding factors often accompanying this disorder [128]. A potential reason for such gait performance differences between dementias is that frontal-temporal networks are more severely and rapidly affected by FTD in the early stages of the disease compared to AD, consequently heightening gait variability of these individuals. Because of the scarceness of literature on gait and FTD, it is still unclear whether other variability parameters are more affected in patients with FTD compared to AD. This warrants further investigations to determine the potential utility of gait variability as an early predictor of disease progression and falls among individuals with FTD.

## Gait Variability and Falls in Parkinson's Disease (PD)

Tremor, rigidity, and slowness are the cardinal symptoms of PD. Gait slowness due to an inability to walk with a normal step length [129] and postural instability [130, 131] can also be present in these individuals. Increased gait variability is already present in the early stages of the disease, and, as PD progresses, motor symptoms

become worse including gait variability [113, 132, 133]. A meta-analysis identified that patients with PD have on average a coefficient of variation for stride time variability above 2.4% [134]. Another meta-analysis [12] found that the stride time variability CV in individuals with PD is on average 2.8% and the stride length variability CV is 5.2%. Although these CVs are modest compared with previous studies in neurologically healthy older adults with a high risk of falls, it is important to note that the impact of PD on gait performance may depend on disease severity and on the disease subtypes. These gait variability differences are clearly observed in the postural instability and gait difficulty (PIGD) subtype as the most affected compared to tremor-dominant (resting tremor, and no clinically identifiable gait and posture problems) subtype [135]. Moreover, the PIGD subtype is more susceptible to have rapid cognitive decline [136] often presenting worse executive function performance at early stages of PD, compared to tremor-dominant patients.

The underlying mechanisms of increased gait variability in PD are not fully clear, but it may be caused by reduced striatal dopamine. Reduced dopaminergic activity can directly affect basal-ganglia functioning, a subcortical structure responsible for controlling internally generated well-learned movements [137]. As mentioned previously in this chapter, high variability is a sign of low movement automaticity. Cross-sectional studies demonstrated that dopaminergic medication intake is effective in decreasing both spatial and temporal gait variability, irrespective of walking direction in patients with PD [138, 139]. An earlier study demonstrated that patients with PD with a history of falls have overall higher stride time variability than non-fallers [140]. This study also showed that dopaminergic medication was able to substantially reduce gait variability in both fallers and non-fallers. Interestingly, even in the medicated state, variability is higher in PD than in controls. This suggests that dopaminergic medications do not fully restore automaticity and/or that other mechanisms are also involved.

Patients with PD with freezing of gait (FOG), defined as an abrupt loss of the ability to generate steps despite the intention to move forward, have an increased risk of falling among patients with PD [141]. Importantly, FOG and falls are two interconnected, yet not completely understood, phenomena in PD [141]. This subtype of patients often have very high temporal and spatial gait variabilities compared with PD non-FOG [140, 142–144] independently of previous falls [145]. Interestingly, patients with FOG have an abnormal increase in gait variability when transitioning from less to more complex terrains including when they approach obstacles [146, 147]. It has been shown that gait instability while approaching obstacles is not dopamine-dependent [148, 149], perhaps due to the nature of the locomotor task (visually guided rather than internally generated). Moreover, worse walking instability is observed in patients with FOG in the few steps before a FOG episode, when an abrupt loss of coordination between agonists' and antagonists' leg muscles is observed [150]. Thus, FOG episodes may be a pathology associated with impairment in the ability to quickly switch from more to less automatic gait control, with the preparation of step adjustments to negotiate terrain changes during navigation, as one example [151, 152]. Interestingly, during these complex locomotor situations, patients with FOG show hyperactive prefrontal areas [153, 154], suggesting that FOG pathology is associated with abnormal levels of higher-order cortical regulation of steps.

While the impact of dopaminergic medication on FOG is still a matter of debate [155] and may differ across patients, some studies showed evidence of significant improvement in gait variability after patients took their regular dosage of dopaminergic medication [142, 156]. Enhancement of dopaminergic activity seems important to maintain gait stability in PD, but the influence on FOG episodes and falls are still questionable. While FOG most often occurs during the “Off” medication state, we do not yet know if falls in people with PD are more common in “Off” (i.e., when gait is typically poorer) or “On” medication state (i.e., when they may be more active and have an increased risk exposure).

Interestingly, not all gait parameters respond to dopaminergic medications in PD [157]. Studies have also shown evidence of significant associations between temporal variability and non-dopaminergic aspects that include reduced cholinergic activity in the brain [158, 159], poor attention, and depression [160–162]. Thus, gait variability and falls in PD have a complex nature since they can be modulated by both dopaminergic and non-dopaminergic pathways. Given the diversity of neural circuitries [163–165] involved with both FOG episodes and gait variability [143, 164, 166–168] in PD, multi- rather than single-domain therapeutic strategies [169] may be more appropriate to treat this disabling locomotor condition. A recent pilot study using electric stimulation of cortical areas using a technique called multi-focal transcranial direct current stimulations (tDCS) supports this idea [170].

---

## Gait Variability and Brain Imaging Correlates

Cortical and subcortical brain areas form a complex neural network that modulate locomotor functions [171, 172]. Hence, it is inaccurate to assume that a single brain area would be responsible for changes in gait performance including variability. A recent literature review showed that several brain areas can be potential neural substrates of increased gait variability [173]. For example, stride-to-stride fluctuations in older adults were associated with structural changes in medial areas important for lower limb coordination and balance. Structural differences in brain areas that process memory, motor execution, cognitive inhibition, well-learned movements, and sensory integration were associated with high temporal and spatial gait variability [173]. In individuals with cognitive impairments and dementia, gait variability was associated with motor cortex, hippocampus, prefrontal cortex, and basal ganglia function [173–175]. In terms of abnormal network functionality, a recent study showed that reduced capacity of the default mode network [176] and the dorsal attentional network to dynamically suppress each other is associated with higher gait variability [177]. These studies suggest that multiple neuroanatomical and cerebral functions play an important role in the gait dynamics of older people.

Real-time measurement of cortical activation in older individuals while walking [178] revealed that those with high prefrontal activation when performing a concurrent mental task had a higher risk to suffer a fall during a 50-month follow-up period, compared with those with lower activation. Stride length variability and prefrontal activation in older adults were both significantly higher during an obstacle

negotiation task compared with unobstructed condition (usual walking) [179]. An abnormal increase in prefrontal activation while performing locomotor tasks may reflect low cognitive efficiency which can be caused by a structural and/or neurochemical decline in the brain due to normal aging [97, 179, 180]. This possibility is consistent with the hyper-prefrontal activation patterns observed in people with PD, in which other neurotransmitters, other than dopamine, can be significantly affected, including acetyl-CoA<sup>1</sup> [99, 181].

---

## Gait Variability and Genotype

Genetic factors including the *ApoE*<sup>2</sup> linked to AD is also associated with poor gait performance [182]. Individuals in pre-dementia stages carrying the *ApoE4* genotype present with higher stride time and length variabilities compared with individuals who do not carry this genotype [183]. Healthy adults who carry the LRRK2-G2019S gene mutation associated with PD also have altered gait patterns including high gait variability, among others, compared with non-carriers, especially under challenging motor-cognitive conditions [184]. The association between genetic factors and gait performance may be indicative of ongoing neurodegenerative process in the brain, particularly in the hippocampus and basal ganglia, both areas responsible for episodic memory and for sustaining motor plans [185]. These studies suggest that changes in gait performance should be considered an earlier expression of AD and PD phenotypes.

---

## Emerging Interventions to Improve Gait Variability

### Rehabilitation Strategies to Improve Gait Variability

The interaction between modifiable and non-modifiable actors discussed earlier in this chapter may determine the severity of gait disturbances in older adults (Table 7.2). High gait variability reflects important declines in structural and physiological functions that cannot only be attributed to normal aging. Hence, therapeutic strategies to prevent abnormal mental and functional deterioration are valuable to maintain or improve gait performance. The next topics will focus specifically on results from therapeutic interventions that impacted gait variability in older adults with and without neurological and neurodegenerative disorders, as well as the potential underlying mechanisms of those walking performance changes.

---

<sup>1</sup>Acetyl-CoA (acetyl coenzyme A) is a molecule that participates in many biochemical reactions involving energy production for cellular functioning including cholinergic transmission. It has a major role in cognitive functioning.

<sup>2</sup>Apolipoprotein E (ApoE) is a class of proteins involved in the metabolism of fats in the body. Individuals expressing the allelic form  $\epsilon 4$ , particularly women, have up to fourfold higher risk to develop Alzheimer's disease compared to allelic forms  $\epsilon 1$ ,  $\epsilon 2$ , and  $\epsilon 3$ . Individuals with two allele  $\epsilon 4$  have 20 times the risk of developing Alzheimer's disease.

**Table 7.2** Summary of stride-to-stride gait variability values assessed during usual walking extracted from multiple studies

Condition	Populations	Age (years) Mean and/or interval across consulted studies	Stride time CV%	Author(s)	Stride length CV%	Author(s)
Aging	Reference values	54	2	[12]	2	[12]
	Reference values	70–74	4	[26]	3 <sup>a</sup>	[26, 27]
	Reference values	75–80	4	[26]	4 <sup>a</sup>	[26, 27]
	Reference values	81–85	3	[26]	4 <sup>a</sup>	[26, 27]
	Reference values	>85	5	[26]	6 <sup>a</sup>	[26, 27]
FoF (older adults)	Non-faller –FoF	81	3	[41]	3	[41]
	Faller –FoF	82	4	[41]	4	[41]
	Non-faller +FoF	81	3	[41]	3	[41]
	Faller +FoF	82	5	[41]	5	[41]
Frailty in older adults	Frail individuals	82	4	[124]	6	[124]
CHF in older adults	Cardiac patients	81	5	[67]	NA	–
Poststroke in older adults	Stroke survivors	61	8	[69]	NA	–
Peripheral neuropathy	Neuropathic older individuals	72 <sup>a</sup> [71–74]	4	[79]	6	[71]
Depression condition	Manifesting depressive symptoms	38	3	[89]	NA	–
<i>ApoE-4</i> carriers	Genetically predisposed to AD	72	3	[183]	3	[183]
<i>LRRK2</i> carriers	Genetically predisposed to PD	54	2	[184]	NA	–
MCI (pre-dementia in older adults)	Amnesic subtype	78 <sup>a</sup> [74–82]	3 <sup>a</sup>	[101, 183]	5 <sup>a</sup>	[105, 183]
	Non-amnesic subtype	78 <sup>a</sup> [74–82]	2	[101]	4 <sup>a</sup>	[105, 183]
AD in older adults	Mild AD	77	4	[119]	6	[117]
	Moderate AD	76 <sup>a</sup> [75–78]	8	[112]	8	[117]
FTD	Behavioral variant	66	8	[128]	NA	–
PD in older adults	PD “On”	62	3	[140]	4	[138]
	PD “Off”	62	4	[140]	5	[138]
	PD –FOG	64	3	[12]	5	[12]
	PD + FOG	64 <sup>a</sup> [63–66]	4	[144]	8 <sup>a</sup>	[145, 156]

*Note.* Rounded stride-to-stride variabilities values extracted from different older populations with risk factors for mobility impairments are presented; CV coefficient of variation, –FoF without fear of falling, +FoF with fear of falling, PD Parkinson’s disease, On under levodopa medication effect, Off not under levodopa medication effect, –FOG without freezing of gait, +FOG with freezing of gait, MCI mild cognitive impairment, AD Alzheimer’s disease, CHF congestive heart failure, LRRK2 leucine-rich repeat kinase 2, ApoE-4 apolipoprotein E, NA no available data

<sup>a</sup>Average calculated from multiple studies

## Physical Interventions

Physical therapies using resistance (e.g., weight lifting) and endurance exercises (e.g., treadmill training) can improve stride time variability [186, 187] and stride length variability [188]. Although physical (exercise) and cognitive (multi-task) therapeutic strategies, isolated or combined, appear to improve gait performance, not all studies have found positive effects [189, 190]. It is unknown whether associations between exercises and gait variability are caused by improved strength and/or coordination in lower limbs. In addition, due to the improved physical fitness after an exercise program and its association with enhancement of cognitive capacity [191], cognitive enhancement could also play an important role in gait variability performance changes. More controlled clinical trials in larger samples are still needed to confirm positive and negative findings.

## Cognitive Interventions

Interventions designed to offer a variety of cognitive challenges seem to improve stride time variability, but these positive effects are only seen when individuals are tested under dual-task conditions [192–194]. Rhythmic stimulation with auditory cues while walking on a treadmill was found to reduce stride time variability in PD [195]. Attentional allocation to relevant external cues during gait plays an important role on improving gait performance of patients with Parkinson's disease, because of difficulties to generate steps through internal volition, even when individuals are distracted by dual tasks [196]. Overall, cognitive training appears to provide cognitive resiliency against multi-task interference on gait stability in normal and neurological populations [197].

Direct cortical stimulation on brain regions involved with higher-order cognitive control, including the prefrontal cortex, using transcranial magnetic stimulation (TMS) techniques appear to decrease both temporal and spatial variabilities in individuals with PD with FOG [198]. A recent study showed that patients with FOG with more preserved ambulatory capabilities, compared with less preserved capabilities, have increased activity in prefrontal areas of the brain during different walking contexts [181]. This result has been interpreted as a compensatory mechanism developed by some patients with FOG to overcome their mobility problems. Notably, another study demonstrated that the combination of different walking interventions that include the addition of task complexities with external demands (e.g., obstacles), a goal-oriented locomotor task that increases prefrontal activation in older adults [99], to conventional treadmill training, benefited gait stability and risk of falls, particularly among individuals at higher risk of falling [98].

## Pharmacological Interventions

Clinical trials that investigated the effects of cognitive enhancers (e.g., cholinergic agonists) in individuals with PD and AD showed a positive impact of these drugs in reducing both temporal and spatial gait variability [119, 199–201]. It is



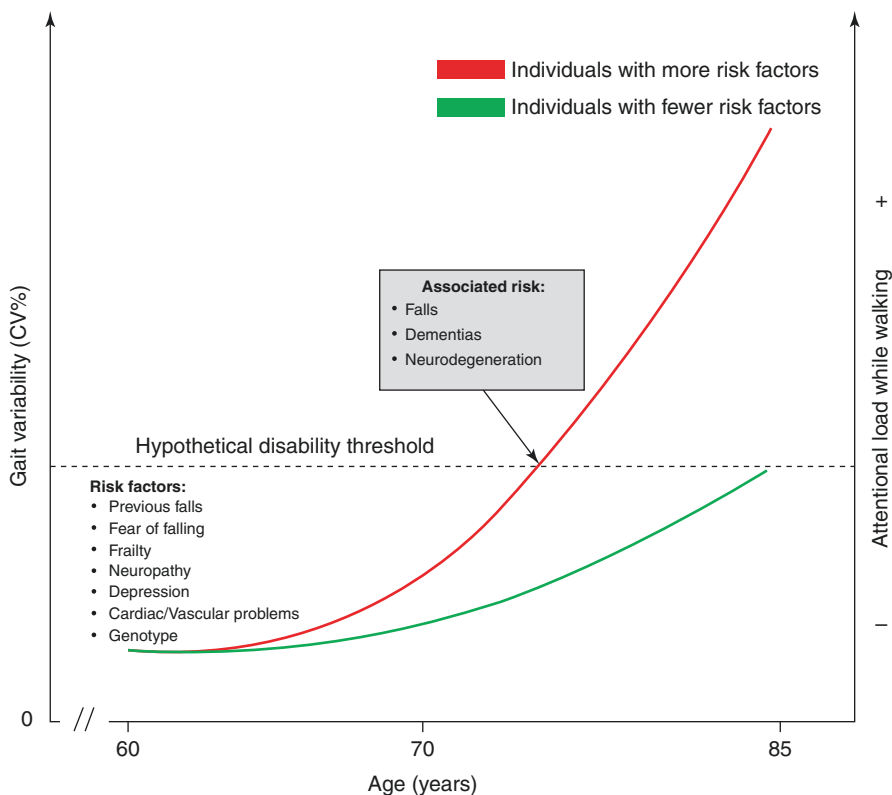
hypothesized that the positive impact of cholinergic agonists on attention and executive functioning would have promoted such positive changes in gait performance. Another pharmacological strategy gaining recognition as a potential treatment for gait disorders is vitamin D supplementation. This is because recent studies have provided evidence that low vitamin D concentration in blood plasma is associated with cognitive deficits and high stride time variability [202, 203]. Results from a randomized controlled trial showed that vitamin D supplementation alone or in combination with physical exercise improved measurements of mobility performance and also decreased the severity of falls (e.g., fewer injuries) in older women [204]. Unfortunately, it is still currently unknown if the positive effects of vitamin D supplementation on falls were mediated via improvements in gait variability since it was not measured. Future studies should also address these questions in both sexes.

## Combinations of Intervention Modalities

Figure 7.3 depicts a multitude of factors contributing to faster variability decline (i.e. worsening) during the aging process. Hence, single interventions may have only limited efficacy in improving gait performance compared with interventions targeting multiple risk factors at once. For example, studies have demonstrated that chronic exposure to exercise routines can improve both physical and executive functioning at the same time [196, 205–209]. Therefore it is difficult to disentangle the mechanisms of such improvements from these interventions since it is difficult to parse apart the effects of physical interventions in cognitive and motor aspects [210, 211]. Difficulties to disentangle the benefits of interventions on gait performance are also observed in pharmacological therapies, including vitamin D supplementation. This is true because vitamin D can act centrally, at the neuronal level by improving synaptic plasticity [212, 213], and/or peripherally [214], at musculoskeletal levels by increasing muscle strength.

While more studies are necessary to disentangle the mechanisms of interventions over cognitive and physical function, the existing literature suggests that combinations of therapeutic modalities may offer superior efficacy to recover function compared with single modalities. For example, it has been hypothesized [215] that physical exercises could nourish neurons by increasing the cerebral blood perfusion and releasing anti-inflammatory agents and neurotrophic factors. Pharmacological interventions could provide the neurochemical substrate for neural growth and synaptic performance, and cognitive training could be important to create new synapses due to requirements in problem-solving capabilities. This approach may be more beneficial as a therapeutic strategy as well as it will enable a better understanding of the pathological mechanisms of mobility dysfunction. Overall, although more controlled clinical trials are necessary, literature available suggests that multi-modality interventions may have superior efficacy to rescue gait performance from rapid decline compared with single modalities, because of its expected broader impact over faulty mobility mechanisms.





**Fig. 7.3** Hypothetical variability curves are displayed based on available normative data and related literature. Note that aging will inevitably increase gait variability (red and green lines), although individuals may never cross the hypothetical disability threshold (dashed line) that indicates an increased risk of disability. Individuals with more comorbidities or risk factors may present faster worsening of gait variability (left Y-axis) over the years compared with individuals with fewer risk factors. For this reason, high gait variability may be considered a strong predictor of disability including falls, dementia, and other neurodegenerative processes. The right Y-axis reflects on the progressive loss of gait automaticity due to a more consciously controlled gait, which is often revealed during multi-tasking situations where the attentional load of the walking context increases

## Concluding Remarks

Gait variability is a sensitive and reliable way to assess gait stability and risk of falls. The decline in gait variability (i.e., high gait variability), but not gait slowness, precedes fall occurrences in many older populations. Because gait variability is a sensitive measure of the risk of falling, but not necessarily specific, it may be helpful to combine different types of variability (e.g., spatial and temporal) with other measures of gait performance to enhance specificity and discriminative abilities for some purposes. Gait variability seems to be a sensitive marker of high-level brain

control over gait performance. Furthermore, high (abnormal) gait variability is associated with brain neurodegenerative processes, which can increase the already high risk of falls, accelerate cognitive decline, and consequently augment the risk of disability among older populations. Given the diversity of factors that can negatively influence gait variability, a combination of interventions may be more effective at rescuing gait stability from abnormal decline than single-modality interventions.

## References

1. Vaughan CL. Theories of bipedal walking: an odyssey. *J Biomech*. 2003;36:513–23.
2. Hausdorff JM, Ladin Z, Wei JY. Footswitch system for measurement of the temporal parameters of gait. *J Biomech* [Internet]. 1995;28(3):347–51. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=7730393](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7730393).
3. Barrett A, O'Connor M, Culhane K, Finucane AM, Mulkerrin E, Lyons D, et al. Accelerometer versus footswitch evaluation of gait unsteadiness and temporal characteristics of gait in two elderly patient groups. *Conf Proc IEEE Eng Med Biol Soc* [Internet]. 2009/01/24. 2008;2008:4527–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19163722>.
4. Beijer TR, Lord SR, Brodie MA. Comparison of handheld video camera and GAITrite(R) measurement of gait impairment in people with early stage Parkinson's disease: a pilot study. *J Park Dis* [Internet]. 2013/08/14. 2013;3(2):199–203. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23938349>.
5. Pfister A, West AM, Bronner S, Noah JA. Comparative abilities of Microsoft Kinect and Vicon 3D motion capture for gait analysis. *J Med Eng Technol*. 2014;38(5):274–80.
6. Ugbohue UC, Papi E, Kaliarntas KT, Kerr A, Earl L, Pomeroy VM, et al. The evaluation of an inexpensive, 2D, video based gait assessment system for clinical use. *Gait Posture*. 2013;38(3):483–9.
7. Costa M, Peng C, Lgoldberger A, Hausdorff J. Multiscale entropy analysis of human gait dynamics. *Phys A Stat Mech Appl*. 2003;330(1–2):53–60.
8. Hausdorff JM. Gait dynamics in Parkinson's disease: common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos* [Internet]. 2009;19(2):26113. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19566273](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19566273).
9. Buzzi UH, Stergiou N, Kurz MJ, Hageman PA, Heidel J. Nonlinear dynamics indicates aging affects variability during gait. *Clin Biomech (Bristol, Avon)* [Internet]. 2003/05/24. 2003;18(5):435–43. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12763440>.
10. Hausdorff JM, Purdon PL, Peng CK, Ladin Z, Wei JY, Goldberger AL. Fractal dynamics of human gait: stability of long-range correlations in stride interval fluctuations. *J Appl Physiol* [Internet]. 1996;80(5):1448–57. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=8727526](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8727526).
11. Hausdorff JM. Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. *Hum Mov Sci* [Internet]. 2007;26(4):555–89. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17618701](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17618701).
12. Moon Y, Sung JH, An R, Hernandez ME, Sosnoff JJ. Gait variability in people with neurological disorders: a systematic review and meta-analysis. *Hum Mov Sci*. 2016;47:197–208.
13. Hollman JH, Childs KB, McNeil ML, Mueller AC, Quilter CM, Youdas JW. Number of strides required for reliable measurements of pace, rhythm and variability parameters of gait during normal and dual task walking in older individuals. *Gait Posture*. 2010;32(1):23–8.

14. Brach J, Berthold R, Craik R, VanSwearingen J, Newman A. Gait variability in community-dwelling older adults. *J Am Geriatr Soc*. 2001;49(12):1646–50.
15. Allali G, Launay CP, Blumen HM, Callisaya ML, De Cock AM, Kressig RW, et al. Falls, cognitive impairment, and gait performance: results from the GOOD initiative. *J Am Med Dir Assoc*. 2017;18(4):335–40.
16. Beauchet O, Allali G, Annweiler C, Bridenbaugh S, Assal F, Kressig RW, et al. Gait variability among healthy adults: low and high stride-to-stride variability are both a reflection of gait stability. *Gerontology* [Internet]. 2009/08/29. 2009;55(6):702–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19713694>.
17. Dhawale AK, Smith MA, Ölveczky BP. The role of variability in motor learning. *Annu Rev Neurosci*. 2017;40(1):479–98.
18. Wu HG, Miyamoto YR, Gonzalez Castro LN, Olveczky BP, Smith MA. Temporal structure of motor variability is dynamically regulated and predicts motor learning ability. *Nat Neurosci* [Internet]. 2014/01/15. 2014;17(2):312–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24413700>.
19. Hausdorff JM, Zeman L, Peng C, Goldberger AL. Maturation of gait dynamics: stride-to-stride variability and its temporal organization in children. *J Appl Physiol* [Internet]. 1999;86(3):1040–7. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10066721](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10066721)
20. Gouelle A, Leroux J, Bredin J, Mégrot F. Changes in gait variability from first steps to adulthood: normative data for the gait variability index. *J Mot Behav*. 2016;48:249.
21. Poldrack RA, Sabb FW, Foerde K, Tom SM, Asarnow RF, Bookheimer SY, et al. The neural correlates of motor skill automaticity. *J Neurosci* [Internet]. 2005;25(22):5356–64. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15930384](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15930384).
22. Arain M, Haque M, Johal L, Mathur P, Nel W, Rais A, et al. Maturation of the adolescent brain. *Neuropsychiatr Dis Treat*. 2013;9:449–61.
23. Chiron C, Raynaud C, Mazière B, Zilbovicius M, Laflamme L, Masure MC, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med*. 1992;33(5):696–703.
24. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc* [Internet]. 2012/11/01. 2012;60(11):2127–36. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23110433>.
25. Hausdorff JM, Edelberg HK, Cudkowicz ME, Singh MA, Wei JY. The relationship between gait changes and falls. *J Am Geriatr Soc* [Internet]. 1997;45(11):1406. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=9361670](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9361670).
26. Hollman JH, McDade EM, Petersen RC. Normative spatiotemporal gait parameters in older adults. *Gait Posture*. 2011;34:111.
27. Oh-Park M, Holtzer R, Xue X, Verghese J. Conventional and robust quantitative gait norms in community-dwelling older adults. *J Am Geriatr Soc*. 2010;58:1512.
28. Lord SR, Ward JA, Williams P, Anstey KJ. Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc* [Internet]. 1994/10/01. 1994;42(10):1110–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7930338>.
29. Hausdorff JM, Herman T, Baltadjieva R, Gurevich T, Giladi N. Balance and gait in older adults with systemic hypertension. *Am J Cardiol* [Internet]. 2003;91(5):643–5. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=12615286](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12615286).
30. Giladi N, Herman T, Reider II G, Gurevich T, Hausdorff JM. Clinical characteristics of elderly patients with a cautious gait of unknown origin. *J Neurol* [Internet]. 2005/02/24. 2005;252(3):300–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15726273>.
31. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil* [Internet]. 2001;82(8):1050–6.

Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11494184](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11494184)

32. Tinetti ME, Mendes de Leon CF, Doucette JT, Baker DI. Fear of falling and fall-related efficacy in relationship to functioning among community-living elders. *J Gerontol* [Internet]. 1994/05/01. 1994;49(3):M140–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8169336>
33. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319(26):1701–7.
34. Florence C, Gwen B, Adam A, Elizabeth B, Judy S, Cynthia D. Medical costs of fatal and nonfatal falls in older adults. *J Am Geriatr Soc*. 2018;0(0).
35. Lord SR, Ward JA, Williams P, Anstey KJ. An epidemiological study of falls in older community-dwelling women: the Randwick falls and fractures study. *Aust J Public Heal* [Internet]. 1993/09/01. 1993;17(3):240–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8286498>.
36. Palvanen M, Kannus P, Parkkari J, Pitkääjärvi T, Pasanen M, Vuori I, et al. The injury mechanisms of osteoporotic upper extremity fractures among older adults: a controlled study of 287 consecutive patients and their 108 controls. *Osteoporos Int*. 2000;11(10):822–31.
37. Stevens JA, Olson S. Reducing falls and resulting hip fractures among older women. *Home Care Provid* [Internet]. 2000/08/10. 2000;5(4):131–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10931397>.
38. Schonnop R, Yang Y, Feldman F, Robinson E, Loughin M, Robinovitch SN. Prevalence of and factors associated with head impact during falls in older adults in long-term care. *CMAJ* [Internet]. 2013/10/09. 2013;185(17):E803–10. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24101612>.
39. Rubenstein LZ, Josephson KR. The epidemiology of falls and syncope. *Clin Geriatr Med* [Internet]. 2002/08/16. 2002;18(2):141–58. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12180240>.
40. Robinovitch SN, Feldman F, Yang Y, Schonnop R, Leung PM, Sarraf T, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet* [Internet]. 2012/10/23. 2013;381(9860):47–54. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23083889>.
41. Maki BE. Gait changes in older adults: predictors of falls or indicators of fear? *J Am Geriatr Soc*. 1997;45(3):313–20.
42. Callisaya ML, Blizzard L, Schmidt MD, Martin KL, Mcginley JL, Sanders LM, et al. Gait, gait variability and the risk of multiple incident falls in older people: a population-based study. *Age Ageing*. 2011;40(4):481–7.
43. Verghese J, Holtzer R, Lipton RB, Wang C. Quantitative gait markers and incident fall risk in older adults. *J Gerontol A Biol Sci Med Sci*. 2009;64A:896.
44. Ijmker T, Lamoth CJ. Gait and cognition: the relationship between gait stability and variability with executive function in persons with and without dementia. *Gait Posture* [Internet]. 2011/10/04. 2012;35(1):126–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21964053>.
45. Kressig RW, Herrmann FR, Grandjean R, Michel J-P, Beauchet O. Gait variability while dual-tasking: fall predictor in older inpatients? *Aging Clin Exp Res*. 2008;20(2):123–30.
46. Herman T, Giladi N, Gurevich T, Hausdorff JM. Gait instability and fractal dynamics of older adults with a “cautious” gait: why do certain older adults walk fearfully? *Gait Posture* [Internet]. 2005/01/11. 2005;21(2):178–85. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15639397>.
47. Ayoubi F, Launay CP, Annweiler C, Beauchet O. Fear of falling and gait variability in older adults: a systematic review and meta-analysis. *J Am Med Dir Assoc* [Internet]. 2014/09/19. 2015;16(1):14–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25230892>.
48. Balash Y, Hadar-Frumer M, Herman T, Peretz C, Giladi N, Hausdorff JM. The effects of reducing fear of falling on locomotion in older adults with a higher level gait disorder. *J*

- Neural Transm [Internet]. 2007/06/20. 2007;114(10):1309–14. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17576513>.
49. Iaboni A, Flint AJ. The complex interplay of depression and falls in older adults: a clinical review. *Am J Geriatr Psychiatry* [Internet]. 2013/04/11. 2013;21(5):484–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23570891>.
  50. Pieruccini-Faria F, Muir-Hunter SW, Montero-Odasso M. Do depressive symptoms affect balance in older adults with mild cognitive impairment? Results from the “gait and brain study”. *Exp Gerontol*. 2018;108:106.
  51. McGrath JC. Fear of falling after brain injury. *Clin Rehabil*. 2008;22(7):635–45.
  52. Johansson J, Nordström A, Nordström P. Greater fall risk in elderly women than in men is associated with increased gait variability during multitasking. *J Am Med Dir Assoc*. 2016;17(6):535–40.
  53. Mirelman A, Herman T, Brozgol M, Dorfman M, Sprecher E, Schweiger A, et al. Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. *PLoS One* [Internet]. 2012/07/07. 2012;7(6):e40297. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22768271>.
  54. Freire RC, Pieruccini-Faria F, Montero-Odasso M. Are human development index dimensions associated with gait performance in older adults? A systematic review. *Exp Gerontol*. 2018;102:59–68.
  55. Zecevic AA, Salmoni AW, Speechley M, Vandervoort AA. Defining a fall and reasons for falling: comparisons among the views of seniors, health care providers, and the research literature. *Gerontologist*. 2006;46:367–76.
  56. Uemura K, Yamada M, Nagai K, Ichihashi N. Older adults at high risk of falling need more time for anticipatory postural adjustment in the precrossing phase of obstacle negotiation. *J Gerontol A Biol Sci Med Sci*. 2011;66A(8):904–9.
  57. Pieruccini-Faria F, Montero-Odasso M. Obstacle negotiation, gait variability and risk of falling. Results from the “Gait and Brain Study”. *J Gerontol A Biol Sci Med Sci*. 2018. in press.
  58. Pieruccini-Faria F, Sarquis-Adamson Y, Montero-Odasso M. Mild cognitive impairment affects obstacle negotiation in older adults: results from “Gait and Brain Study”. *Gerontology*. 2018;1–10.
  59. Barkley RA. The executive functions and self-regulation: an evolutionary neuropsychological perspective. *Neuropsychol Rev* [Internet]. 2001/06/08. 2001;11(1):1–29. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11392560>.
  60. Ayoubi F, Launay CP, Kabeshova A, Fantino B, Annweiler C, Beauchet O. The influence of fear of falling on gait variability: results from a large elderly population-based cross-sectional study. *J Neuroeng Rehabil* [Internet]. 2014/08/30. 2014;11:128. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25168467>.
  61. Carey BJ, Potter JF. Cardiovascular causes of falls. *Age Ageing*. 2001;30:19.
  62. Tan MP, Kenny RA. Cardiovascular assessment of falls in older people. *Clin Interv Aging*. 2006;1:57.
  63. Bhangu J, King-Kallimanis BL, Donoghue OA, Carroll L, Kenny RA. Falls, non-accidental falls and syncope in community-dwelling adults aged 50 years and older: implications for cardiovascular assessment. *PLoS One*. 2017;12:e0180997.
  64. Myers SA, Johanning JM, Stergiou N, Celis RI, Robinson L, Pipinos II. Gait variability is altered in patients with peripheral arterial disease. *J Vasc Surg*. 2009;49:924.
  65. Angelousi A, Girerd N, Benetos A, Frimat L, Gautier S, Weryha G, et al. Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis. *J Hypertens*. 2014;32:1562.
  66. Helbostad JL, Leirfall S, Moe-Nilssen R, Sletvold O. Physical fatigue affects gait characteristics in older persons. *J Gerontol A Biol Sci Med Sci*. 2007;62:1010.
  67. Hausdorff JM, Forman DE, Ladin Z, Goldberger AL, Rigney DR, Wei JY. Increased walking variability in elderly persons with congestive heart failure. *J Am Geriatr Soc*. 1994;42:1056.

68. Balasubramanian CK, Neptune RR, Kautz SA. Variability in spatiotemporal step characteristics and its relationship to walking performance post-stroke. *Gait Posture*. 2009;29:408.
69. Plummer-D'Amato P, Altmann LJP, Saracino D, Fox E, Behrman AL, Marsiske M. Interactions between cognitive tasks and gait after stroke: a dual task study. *Gait Posture*. 2008;27:683.
70. Chisholm AE, Makepeace S, Inness EL, Perry SD, McIlroy WE, Mansfield A. Spatial-temporal gait variability poststroke: variations in measurement and implications for measuring change. *Arch Phys Med Rehabil*. 2014;95:1335.
71. Roman De Mettelinge T, Delbaere K, Calders P, Gysel T, Van Den Noortgate N, Cambier D. The impact of peripheral neuropathy and cognitive decrements on gait in older adults with type 2 diabetes mellitus. *Arch Phys Med Rehabil*. 2013;94:1074.
72. Thies SB, Richardson JK, DeMott T, Ashton-Miller JA. Influence of an irregular surface and low light on the step variability of patients with peripheral neuropathy during level gait. *Gait Posture*. 2005;22(1):40–5.
73. Richardson JK, Thies SB, DeMott TK, Ashton-Miller JA. Interventions improve gait regularity in patients with peripheral neuropathy while walking on an irregular surface under low light. *J Am Geriatr Soc*. 2004;52(4):510–5.
74. Richardson JK, Thies S, Ashton-Miller JA. An exploration of step time variability on smooth and irregular surfaces in older persons with neuropathy. *Clin Biomech*. 2008;23(3):349–56.
75. Richardson JK, Thies SB, TK DM, Ashton-Miller JA. A comparison of gait characteristics between older women with and without peripheral neuropathy in standard and challenging environments. *J Am Geriatr Soc*. 2004;52:1532.
76. DeMott TK, Richardson JK, Thies SB, Ashton-Miller JA. Falls and gait characteristics among older persons with peripheral neuropathy. *Am J Phys Med Rehabil*. 2007;86(2):125–32.
77. Redfern MS, Jennings JR, Martin C, Furman JM. Attention influences sensory integration for postural control in older adults. *Gait Posture* [Internet]. 2001/10/16. 2001;14(3):211–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11600324>.
78. Redfern MS, Talkowski ME, Jennings JR, Furman JM. Cognitive influences in postural control of patients with unilateral vestibular loss. *Gait Posture* [Internet]. 2004/03/12. 2004;19(2):105–14. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15013498>.
79. Wuehr M, Schniepp R, Schlick C, Huth S, Pradhan C, Dieterich M, et al. Sensory loss and walking speed related factors for gait alterations in patients with peripheral neuropathy. *Gait Posture*. 2014;39:852.
80. Beekman ATF, Copeland JRM, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry*. 1999;174:307.
81. Sachdev P, Aniss AM. Slowness of movement in melancholic depression. *Biol Psychiatry* [Internet]. 1994/02/15. 1994;35(4):253–62. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8186330>.
82. Michalak J, Troje NF, Fischer J, Vollmar P, Heidenreich T, Schulte D. Embodiment of sadness and depression--gait patterns associated with dysphoric mood. *Psychosom Med* [Internet]. 2009/05/06. 2009;71(5):580–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19414617>.
83. Whooley MA, Kip KE, Cauley JA, Ensrud KE, Nevitt MC, Browner WS. Depression, falls, and risk of fracture in older women. Study of Osteoporotic Fractures Research Group. *Arch Intern Med* [Internet]. 1999/03/13. 1999;159(5):484–90. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10074957>.
84. Wei TS, Liu PT, Chang LW, Liu SY. Gait asymmetry, ankle spasticity, and depression as independent predictors of falls in ambulatory stroke patients. *PLoS One* [Internet]. 2017/05/26. 2017;12(5):e0177136. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28542281>.
85. Turcu A, Toubin S, Mourey F, D'Athis P, Manckoundia P, Pfitzenmeyer P. Falls and depression in older people. *Gerontology* [Internet]. 2004/08/28. 2004;50(5):303–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15331859>.
86. Radovanovic S, Jovicic M, Maric NP, Kostic V. Gait characteristics in patients with major depression performing cognitive and motor tasks while walking. *Psychiatry Res*



- [Internet]. 2014/03/13. 2014;217(1–2):39–46. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24613201>.
87. Gabel NM, Crane NA, Avery ET, Kay RE, Laurent A, Giordani B, et al. Dual-tasking gait variability and cognition in late-life depression. *Int J Geriatr Psychiatry* [Internet]. 2015/08/08. 2015;30(11):1120–8. Available from.: <http://www.ncbi.nlm.nih.gov/pubmed/26251013>.
  88. Brandler TC, Wang C, Oh-Park M, Holtzer R, Verghese J. Depressive symptoms and gait dysfunction in the elderly. *Am J Geriatr Psychiatry* [Internet]. 2011/03/23. 2012;20(5):425–32. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21422907>.
  89. Hausdorff JM, Peng CK, Goldberger AL, Stoll AL. Gait unsteadiness and fall risk in two affective disorders: a preliminary study. *BMC Psychiatry* [Internet]. 2004;4:39. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15563372](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15563372).
  90. Martin KL, Blizzard L, Wood AG, Srikanth V, Thomson R, Sanders LM, et al. Cognitive function, gait, and gait variability in older people: a population-based study. *J Gerontol A Biol Sci Med Sci*. 2013;
  91. van Iersel MB, Kessels RPC, Bloem BR, Verbeek ALM, Olde Rikkert MGM. Executive functions are associated with gait and balance in community-living elderly people. *J Gerontol A Biol Sci Med Sci*. 2008;63(12):1344.
  92. Ijmker T, Lamoth CJC. Gait and cognition: the relationship between gait stability and variability with executive function in persons with and without dementia. *Gait Posture*. 2012;35(1):126–30.
  93. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci* [Internet]. 2010/05/21. 2010;65(10):1086–92. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20484336>.
  94. Graveson J, Bauermeister S, McKeown D, Bunce D. Intraindividual reaction time variability, falls, and gait in old age: a systematic review. *J Gerontol B Psychol Sci Soc Sci*. 2016;71:857–64.
  95. Sukits AL, Nebes RD, Chambers AJ, Ledgerwood A, Halligan EM, Perera S, et al. Intraindividual variability in gait and in cognitive performance are not related in the elderly. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2014;21(3):283–95.
  96. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing* [Internet]. 2012/03/01. 2012;41(3):299–308. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22374645>.
  97. Maidan I, Eyal S, Kurz I, Geffen N, Gazit E, Ravid L, et al. Age-associated changes in obstacle negotiation strategies: does size and timing matter? *Gait Posture*. 2018;59:242–7.
  98. Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet*. 2016;388(10050):1170–82.
  99. Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, Hausdorff JM. Effects of aging on prefrontal brain activation during challenging walking conditions. *Brain Cogn*. 2017;115:41–6.
  100. Allali G, Assal F, Kressig RW, Dubost V, Herrmann FR, Beauchet O. Impact of impaired executive function on gait stability. *Dement Geriatr Cogn Disord*. 2008;26(4):364–9.
  101. Montero-Odasso M, Oteng-Amoako A, Speechley M, Gopaul K, Beauchet O, Annweiler C, et al. The motor signature of mild cognitive impairment: results from the gait and brain study. *J Gerontol A Biol Sci Med Sci* [Internet]. 2014/09/04. 2014;69(11):1415–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25182601>.
  102. Tyrovolas S, Koyanagi A, Lara E, Ivan Santini Z, Haro JM. Mild cognitive impairment is associated with falls among older adults: Findings from the Irish Longitudinal Study on Ageing (TILDA). *Exp Gerontol* [Internet]. 2015/12/29. 2015;75:42–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26707711>.

103. Delbaere K, Kochan NA, Close JCT, Menant JC, Sturnieks DL, Brodaty H, et al. Mild cognitive impairment as a predictor of falls in community-dwelling older people. *Am J Geriatr Psychiatry*. 2012;20(10):845–53.
104. Petersen RC. Clinical practice. Mild cognitive impairment. *N Engl J Med* [Internet]. 2011;364(23):2227–34. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21651394>.
105. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, et al. Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc*. 2008;56:1244.
106. Hausdorff JM, Yogev G, Springer S, Simon ES, Giladi N. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res* [Internet]. 2005;164(4):541–8. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15864565](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15864565).
107. Savica R, Wennberg AMV, Hagen C, Edwards K, Roberts RO, Hollman JH, et al. Comparison of gait parameters for predicting cognitive decline: the Mayo Clinic study of aging. *J Alzheimers Dis*. 2017;55:559.
108. Martin K, Thomson R, Blizzard L, Wood A, Garry M, Srikanth V. Visuospatial ability and memory are associated with falls risk in older people. *Dement Geriatr Cogn Disord*. 2009;27(5):451–7.
109. van Schoor NM, Smit JH, Pluijm SM, Jonker C, Lips P. Different cognitive functions in relation to falls among older persons. Immediate memory as an independent risk factor for falls. *J Clin Epidemiol*. 2002;55(9):855–62.
110. Trujillo AJ, Hyder AA, Steinhardt LC. Cognitive functioning and the probability of falls among seniors in Havana, Cuba. *Int J Aging Hum Dev*. 2011;73(2):175–94.
111. Holtzer R, Friedman R, Lipton RB, Katz M, Xue X, Vergese J. The relationship between specific cognitive functions and falls in aging. *Neuropsychology*. 2012;21(5):540–8.
112. Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. *J Am Geriatr Soc* [Internet]. 2003;51(11):1633–7. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=14687395](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14687395).
113. Hausdorff JM, Cudkowicz ME, Firtion R, Wei JY, Goldberger AL. Gait variability and basal ganglia disorders: stride-to-stride variations of gait cycle timing in Parkinson's disease and Huntington's disease. *Mov Disord* [Internet]. 1998;13(3):428–37. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=9613733](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9613733).
114. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet*. 2011;377(9770):1019–31.
115. Ben-Shlomo Y, Sieradzan K. Idiopathic Parkinson's disease: epidemiology, diagnosis and management. *Br J Gen Pr* [Internet]. 1995;05/01. 1995;45(394):261–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7619574>.
116. Fargo K. Alzheimer's Association report: 2014 Alzheimers disease facts and figures. *Alzheimers Dement*. 2014;10(2):e47.
117. Nakamura T, Meguro K, Sasaki H. Relationship between falls and stride length variability in senile dementia of the alzheimer type. *Gerontology*. 1996;42(2):108–13.
118. Annweiler C, Beauchet O, Celle S, Roche F, Annweiler T, Allali G, et al. Contribution of brain imaging to the understanding of gait disorders in Alzheimer's disease: a systematic review. *Am J Alzheimers Dis Other Dement* [Internet]. 2012;08/30. 2012;27(6):371–80. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22930697>.
119. Montero-Odasso M, Muir-Hunter SW, Oteng-Amoako A, Gopaul K, Islam A, Borrie M, et al. Donepezil improves gait performance in older adults with mild Alzheimer's disease: a phase II clinical trial. *J Alzheimers Dis* [Internet]. 2014;08/01. 2015;43(1):193–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25079803>.
120. Muir SW, Speechley M, Wells J, Borrie M, Gopaul K, Montero-Odasso M. Gait assessment in mild cognitive impairment and Alzheimer's disease: the effect of dual-task challenges



- across the cognitive spectrum. *Gait Posture* [Internet]. 2011/09/24. 2012;35(1):96–100. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21940172>.
121. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41:299–308.
  122. Montero-Odasso M, Muir SW, Speechley M. Dual-task complexity affects gait in people with mild cognitive impairment: the interplay between gait variability, dual tasking, and risk of falls. *Arch Phys Med Rehabil* [Internet]. 2012/02/01. 2012;93(2):293–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22289240>.
  123. van Iersel MB, Verbeek ALM, Bloem BR, Munneke M, Esselink RA, Rikkert MGMO. Frail elderly patients with dementia go too fast. *J Neurol Neurosurg Psychiatry*. 2006;77(7):874–6.
  124. Montero-Odasso M, Muir SW, Hall M, Doherty TJ, Kloseck M, Beauchet O, et al. Gait variability is associated with frailty in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* [Internet]. 2011/03/02. 2011;66(5):568–76. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21357190>.
  125. Montero-Odasso M, Casas A, Hansen KT, Bilski P, Gutmanis I, Wells JL, et al. Quantitative gait analysis under dual-task in older people with mild cognitive impairment: a reliability study. *J Neuroeng Rehabil* [Internet]. 2009/09/24. 2009;6:35. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19772593>.
  126. Bang J, Spina S, Miller BL. Non-Alzheimer's dementia I: Frontotemporal dementia. *Lancet*. 2015;386:1672.
  127. Cardoso F, Hodges J, Evans AH, Revesz T, Williams DR. Postural instability, frontotemporal dementia, and ophthalmoplegia: Clinicopathological case. *Mov Disord*. 2011;26:1808.
  128. Allali G, Dubois B, Assal F, Lallart E, De Souza LC, Bertoux M, et al. Frontotemporal dementia: pathology of gait? *Mov Disord*. 2010;25:731.
  129. Morris ME, Insek R, Matyas TA, Summers JJ. The pathogenesis of gait hypokinesia in Parkinson's disease. *Brain* [Internet]. 1994;117 ( Pt 5):1169–81. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=7953597](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7953597).
  130. Barbieri FA, Rinaldi NM, Santos PC, Lirani-Silva E, Vitorio R, Teixeira-Arroyo C, et al. Functional capacity of Brazilian patients with Parkinson's disease (PD): relationship between clinical characteristics and disease severity. *Arch Gerontol Geriatr* [Internet]. 2011/10/04. 2012;54(2):e83–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21963176>.
  131. Horak FB, Dimitrova D, Nutt JG. Direction-specific postural instability in subjects with Parkinson's disease. *Exp Neurol* [Internet]. 2005/05/05. 2005;193(2):504–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15869953>.
  132. Montero-Odasso MM, Sarquis-Adamson Y, Speechley M, Borrie MJ, Hachinski VC, Wells J, et al. Association of dual-task gait with incident dementia in mild cognitive impairment: results from the gait and brain study. *JAMA Neurol*. 2017;74(7):857–65.
  133. Galna B, Lord S, Burn DJ, Rochester L. Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. *Mov Disord*. 2015;30(3):359–67.
  134. König N, Singh NB, Baumann CR, Taylor WR. Can gait signatures provide quantitative measures for aiding clinical decision-making? A systematic meta-analysis of gait variability behavior in patients with Parkinson's disease. *Front Hum Neurosci*. 2016;10:319.
  135. Herman T, Weiss A, Brozgol M, Giladi N, Hausdorff JM. Gait and balance in Parkinson's disease subtypes: objective measures and classification considerations. *J Neurol*. 2014;261(12):2401.
  136. Kawada T. Predictors of dementia in Parkinson disease: a prospective cohort study. *Neurology*. 2015;84:1285.
  137. Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. *Brain* [Internet]. 2005/06/17. 2005;128(Pt 10):2250–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15958505>.

138. Bryant MS, Rintala DH, Hou JG, Collins RL, Protas EJ. Gait variability in Parkinson's disease: Levodopa and walking direction. *Acta Neurol Scand*. 2016;134:83–6.
139. Bryant MS, Rintala DH, Hou JG, Lai EC, Protas EJ. Effects of levodopa on forward and backward gait patterns in persons with Parkinson's disease. *NeuroRehabilitation*. 2011;29(3):247–52.
140. Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM. Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. *J Neurol Sci*. 2003;212(1–2):47–53.
141. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of Gait in Parkinson's disease: a review of two interconnected, episodic phenomena. *Mov Disord*. 2004;19:871–84.
142. Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. *Eur J Neurol* [Internet]. 2003;10(4):391–8. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=12823491](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12823491).
143. Pieruccini-Faria F, Ehgoetz Martens KA, Silveira CR, Jones JA, Almeida QJ. Side of basal ganglia degeneration influences freezing of gait in Parkinson's disease. *Behav Neurosci* [Internet]. 2015/03/03. 2015;129(2):214–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25730121>.
144. Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. *Exp Brain Res* [Internet]. 2003/03/01. 2003;149(2):187–94. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12610686>.
145. Shah J, Pillai L, Williams DK, Doerhoff SM, Larson-Prior L, Garcia-Rill E, et al. Increased foot strike variability in Parkinson's disease patients with freezing of gait. *Parkinsonism Relat Disord*. 2018;53:58.
146. Pieruccini-Faria F, Jones JA, Almeida QJ. Motor planning in Parkinson's disease patients experiencing freezing of gait: the influence of cognitive load when approaching obstacles. *Brain Cogn* [Internet]. 2014/04/15. 2014;87:76–85. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24727559>.
147. Almeida QJ, Lebold CA. Freezing of gait in parkinson's disease: a perceptual cause for a motor impairment? *J Neurol Neurosurg Psychiatry* [Internet]. 2009; Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19758982](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19758982).
148. Pieruccini-Faria F, Vitorio R, Almeida QJ, Silveira CR, Caetano MJ, Stella F, et al. Evaluating the acute contributions of dopaminergic replacement to gait with obstacles in Parkinson's disease. *J Mot Behav* [Internet]. 2013/07/10. 2013;45(5):369–80. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23834709>.
149. Pieruccini-Faria F, Jones JA, Almeida QJ. Insight into dopamine-dependent planning deficits in Parkinson's disease: a sharing of cognitive & sensory resources. *Neuroscience* [Internet]. 2016/01/23. 2016;318:219–29. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26794593>.
150. Nieuwboer A, Dom R, De Weerd W, Desloovere K, Janssens L, Stijn V. Electromyographic profiles of gait prior to onset of freezing episodes in patients with Parkinson's disease. *Brain* [Internet]. 2004/05/07. 2004;127(Pt 7):1650–60. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15128621>.
151. Silveira CRA, Ehgoetz Martens KA, Pieruccini-Faria F, Bell-Boucher D, Roy EA, Almeida QJ. Disentangling perceptual judgment and online feedback deficits in Parkinson's freezing of gait. *J Neurol*. 2015;262(7):1629–36.
152. Bhatt H, Pieruccini-Faria F, Almeida QJ. Dynamics of turning sharpness influences freezing of gait in Parkinson's disease. *Park Relat Disord* [Internet]. 2012/10/23. 2013;19(2):181–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23083513>.
153. Maidan I, Bernad-Elazari H, Gazit E, Giladi N, Hausdorff JM, Mirelman A. Changes in oxygenated hemoglobin link freezing of gait to frontal activation in patients with Parkinson dis-

- ease: an fNIRS study of transient motor-cognitive failures. *J Neurol* [Internet]. 2015/02/01. 2015; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25636682>.
154. Maidan I, Bernad-Elazari H, Gazit E, Mirelman A, Hausdorff J, Giladi N. Increased activation of the frontal lobe is associated with freezing of gait in patients with Parkinson's disease: an fNIRS study (P6.074). *Neurology*. 2015;84(14 Supplement):P6.074.
155. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. *Lancet Neurol* [Internet]. 2011/07/23. 2011;10(8):734–44. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21777828>.
156. Barbe MT, Amarell M, Snijders AH. Gait and upper limb variability in Parkinson's disease patients with and without freezing of gait. *J Neurol*. 2014;261(2):330–42.
157. Curtze C, Nutt JG, Carlson-Kuhta P, Mancini M, Horak FB. Levodopa is a Double-Edged Sword for balance and gait in people with Parkinson's disease. *Mov Disord* [Internet]. 2015/06/23. 2015;30(10):1361–70. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26095928>.
158. Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. *Behav Brain Res* [Internet]. 2010/01/12. 2011;221(2):564–73. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20060022>.
159. Bohnen NI, Muller ML, Koeppe RA, Studenski SA, Kilbourn MA, Frey KA, et al. History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology* [Internet]. 2009/11/18. 2009;73(20):1670–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19917989>.
160. Bohnen NI, Frey KA, Studenski S, Kotagal V, Koeppe RA, Scott PJ, et al. Gait speed in Parkinson disease correlates with cholinergic degeneration. *Neurology* [Internet]. 2013/10/01. 2013;81(18):1611–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24078735>.
161. Rochester L, Yarnall AJ, Baker MR, David R V, Lord S, Galna B, et al. Cholinergic dysfunction contributes to gait disturbance in early Parkinson's disease. *Brain* [Internet]. 2012/09/11. 2012;135(Pt 9):2779–88. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22961550>.
162. Lord S, Baker K, Nieuwboer A, Burn D, Rochester L. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? *J Neurol* [Internet]. 2010/11/06. 2011;258(4):566–72. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21052710>.
163. Ehgoetz Martens KA, Hall JM, Georgiades MJ, Gilat M, Walton CC, Matar E, et al. The functional network signature of heterogeneity in freezing of gait. *Brain*. 2018;141:1145.
164. Gilat M, Shine JM, Bolitho SJ, Matar E, Kamsma YP, Naismith SL, et al. Variability of Stepping during a Virtual Reality Paradigm in Parkinson's Disease Patients with and without Freezing of Gait. *PLoS One* [Internet]. 2013/06/28. 2013;8(6):e66718. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23805270>.
165. Shine JM, Matar E, Ward PB, Bolitho SJ, Gilat M, Pearson M, et al. Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease. *Brain* [Internet]. 2013/03/15. 2013;136(Pt 4):1204–15. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23485851>.
166. Ehgoetz Martens KA, Pieruccini-Faria F, Silveira CR, Almeida QJ. The contribution of optic flow to freezing of gait in left- and right-PD: different mechanisms for a common phenomenon? *Park Relat Disord* [Internet]. 2013/07/31. 2013;19(11):1046–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23891343>.
167. Vercruyse S, Devos H, Munks L, Spildooren J, Vandenbossche J, Vandenberghe W, et al. Explaining freezing of gait in Parkinson's disease: motor and cognitive determinants. *Mov Disord* [Internet]. 2012/11/02. 2012;27(13):1644–51. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23115014>.
168. Ehgoetz Martens KA, Pieruccini-Faria F, Almeida QJ. Could sensory mechanisms be a core factor that underlies freezing of gait in Parkinson's disease? *PLoS One* [Internet]. 2013/05/15. 2013;8(5):e62602. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23667499>.

169. Belghali M, Chastan N, Davenne D, Decker LM. Improving dual-task walking paradigms to detect prodromal Parkinson's and Alzheimer's diseases. *Front Neurol*. 2017;8:207.
170. Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, et al. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. *Mov Disord*. 2018;33:642.
171. Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. *Mov Disord* [Internet]. 2013/10/18. 2013;28(11):1483–91. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24132836>.
172. Takakusaki K, Oohinata-Sugimoto J, Saitoh K, Habaguchi T. Role of basal ganglia-brainstem systems in the control of postural muscle tone and locomotion. *Prog Brain Res* [Internet]. 2003/12/05. 2004;143:231–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14653168>.
173. Tian Q, Chastan N, Bair WN, Resnick SM, Ferrucci L, Studenski SA. The brain map of gait variability in aging, cognitive impairment and dementia—a systematic review. *Neurosci Biobehav Rev*. 2017;74:149–62.
174. Annweiler C, Montero-Odasso M, Bartha R, Drozd J, Hachinski V, Beauchet O. Association between gait variability and brain ventricle attributes: a brain mapping study. *Exp Gerontol* [Internet]. 2014/06/28. 2014;57:256–63. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24971908>.
175. Annweiler C, Beauchet O, Bartha R, Wells JL, Borrie MJ, Hachinski V, et al. Motor cortex and gait in mild cognitive impairment: a magnetic resonance spectroscopy and volumetric imaging study. *Brain* [Internet]. 2013/02/26. 2013;136(Pt 3):859–71. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23436505>.
176. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008;1124:1–38.
177. Lo O-Y, Halko MA, Zhou J, Harrison R, Lipsitz LA, Manor B. Gait speed and gait variability are associated with different functional brain networks. *Front Aging Neurosci*. 2017;9
178. Verghese J, Wang C, Ayers E, Izzetoglu M, Holtzer R. Brain activation in high-functioning older adults and falls: prospective cohort study. *Neurology*. 2017;88(2):191–7.
179. Maidan I, Shustak S, Sharon T, Bernad-Elazari H, Geffen N, Giladi N, et al. Prefrontal cortex activation during obstacle negotiation: what's the effect size and timing? *Brain Cogn*. 2018;
180. Nieuwhof F, Reelick M, Rikkert MO, Mirelman A, Hausdorff J, Claassen J. Wireless fNIRS for neuroimaging during dual task walking and obstacle negotiation in the elderly: feasible, reliable and valid? *Eur Geriatr Med*. 2012;3:54.
181. Maidan I, Bernad-Elazari H, Giladi N, Hausdorff JM, Mirelman A. When is higher level cognitive control needed for locomotor tasks among patients with Parkinson's disease? *Brain Topogr*. 2017;30(4):531–8.
182. Verghese J, Holtzer R, Wang C, Katz MJ, Barzilai N, Lipton RB. Role of APOE genotype in gait decline and disability in aging. *J Gerontol A Biol Sci Med Sci*. 2013;68(11):1395–401.
183. Sakurai R, Montero-Odasso M. Apolipoprotein E4 Allele and Gait performance in mild cognitive impairment: results from the Gait and Brain Study. *J Gerontol A Biol Sci Med Sci*. 2017;72(12):1676–82.
184. Mirelman A, Gurevich T, Giladi N, Bar-Shira A, Orr-Urtreger A, Hausdorff JM. Gait alterations in healthy carriers of the LRRK2 G2019S mutation. *Ann Neurol*. 2011;69(1):193–7.
185. Allali G, van der Meulen M, Beauchet O, Rieger SW, Vuilleumier P, Assal F. The neural basis of age-related changes in motor imagery of gait: an fMRI study. *J Gerontol A Biol Sci Med Sci* [Internet]. 2013/12/26. 2014;69(11):1389–98. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24368777>.
186. Hausdorff JM, Nelson ME, Kaliton D, Layne JE, Bernstein MJ, Nuernberger A, et al. Etiology and modification of gait instability in older adults: a randomized controlled trial of exercise. *J Appl Physiol* [Internet]. 2001;90(6):2117–29. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11356774](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11356774).

187. Wayne PM, Hausdorff JM, Lough M, Gow BJ, Lipsitz L, Novak V, et al. Tai Chi training may reduce dual task gait variability, a potential mediator of fall risk, in healthy older adults: cross-sectional and randomized trial studies. *Front Hum Neurosci*. 2015;9:332.
188. Wang R-Y, Wang Y-L, Cheng F-Y, Chao Y-H, Chen C-L, Yang Y-R. Effects of combined exercise on gait variability in community-dwelling older adults. *Age (Dordr)*. 2015;37(3):9780.
189. Gardner MM, Robertson MC, Campbell AJ. Exercise in preventing falls and fall related injuries in older people: a review of randomised controlled trials. *Br J Sports Med*. 2000;34(1):7–17.
190. Dean CM, Rissel C, Sherrington C, Sharkey M, Cumming RG, Lord SR, et al. Exercise to enhance mobility and prevent falls after stroke: the community stroke club randomized trial. *Neurorehabil Neural Repair*. 2012;26(9):1046–57.
191. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14(2):125–30.
192. Yogeve-Seligmann G, Giladi N, Brozgov M, Hausdorff JM. A training program to improve gait while dual tasking in patients with Parkinson's disease: a pilot study. *Arch Phys Med Rehabil*. 2012;93(1):176–81.
193. Beauchet O, Launay C, Annweiler C, Fantino B, Allali G, De Decker L. Physical training-related changes in gait variability while single and dual tasking in older adults: magnitude of gait variability at baseline matters. *Eur J Phys Rehabil Med*. 2013;49(6):857–64.
194. Steinmetz JP, Federspiel C. The effects of cognitive training on gait speed and stride variability in old adults: findings from a pilot study. *Aging Clin Exp Res*. 2014;26(6):635–43.
195. Frenkel-Toledo S, Giladi N, Peretz C, Herman T, Gruendlinger L, Hausdorff JM. Treadmill walking as an external pacemaker to improve gait rhythm and stability in Parkinson's disease. *Mov Disord [Internet]*. 2005;20(9):1109–14. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15929090](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15929090).
196. Beck EN, Intzandt BN, Almeida QJ. Can dual task walking improve in Parkinson's disease after external focus of attention exercise? A single blind randomized controlled trial. *Neurorehabil Neural Repair*. 2017; <https://doi.org/10.1177/154596831774678>.
197. Intzandt B, Beck EN, Silveira CRA. The effects of exercise on cognition and Gait in Parkinson's disease: a scoping review. *Neurosci Biobehav Rev*. 2018;95:136.
198. Dagan M, Herman T, Mirelman A, Giladi N, Hausdorff JM. The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study. *Exp Brain Res*. 2017;235(8):2463–72.
199. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin Neuropharmacol [Internet]*. 2006;29(1):15–7. Available from: [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16518128](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16518128).
200. Beauchet O, Launay CP, Montero-Odasso M, Annweiler C, Allali G. Anti-dementia drugs-related changes in gait performance while single and dual tasking in patients with Alzheimer disease: a meta-analysis. *Curr Alzheimer Res [Internet]*. 2015/07/15. 2015;12(8):761–71. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26159199>.
201. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JCT, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPOND): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016.
202. Beauchet O, Annweiler C, Verghese J, Fantino B, Herrmann FR, Allali G. Biology of gait control: vitamin D involvement. *Neurology [Internet]*. 2011/04/08. 2011;76(19):1617–22. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21471466>.
203. Annweiler C, Montero-Odasso M, Llewellyn DJ, Richard-Devantoy S, Duque G, Beauchet O. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. *J Alzheimers Dis [Internet]*. 2013/08/21. 2013;37(1):147–71. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23948884>.

204. Uusi-Rasi K, Patil R, Karinkanta S, Kannus P, Tokola K, Lamberg-Allardt C, et al. A 2-year follow-up after a 2-year RCT with vitamin D and exercise: effects on falls, injurious falls and physical functioning among older women. *J Gerontol A Biol Sci Med Sci*. 2017;72(9):1239–45.
205. Liu-Ambrose T, Donaldson MG. Exercise and cognition in older adults: is there a role for resistance training programmes? *Br J Sports Med*. 2009;43:25–7.
206. Liu-Ambrose T. Resistance training and executive functions. *Arch Intern Med*. 2010;170(2):170.
207. Silveira CRA, Roy EA, Intzandt BN, Almeida QJ. Aerobic exercise is more effective than goal-based exercise for the treatment of cognition in Parkinson's disease. *Brain Cogn*. 2018;122:1–8.
208. Tanaka K, de Quadros AC, Santos RF, Stella F, Gobbi LTB, Gobbi S. Benefits of physical exercise on executive functions in older people with Parkinson's disease. *Brain Cogn*. 2009;69(2):435–41.
209. Silveira CRA, Roy EA, Almeida QJ. Acute effects of aerobic exercise on cognitive function in individuals with Parkinson's disease. *Neurosci Lett*. 2018;671:60–5.
210. Montero-Odasso M. Falls as a geriatric syndrome: how to prevent them? How to treat them? In: *Osteoporosis in older persons*; 2009. p. 110–25.
211. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: implications for risk assessment and prevention. *J Am Geriatr Soc*. 2018;66(2):367–75.
212. Morley JE. Does vitamin D modulate cognition? *Nat Rev Neurol*. 2014;10:613.
213. Latimer CS, Brewer LD, Searcy JL, Chen K-C, Popović J, Kraner SD, et al. Vitamin D prevents cognitive decline and enhances hippocampal synaptic function in aging rats, *Proc Natl Acad Sci U S A*. 2014;111:E4359.
214. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* [Internet]. 2011/12/23. 2011;59(12):2291–300. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22188076>.
215. Bamidis PD, Vivas AB, Styliadis C, Frantzidis C, Klados M, Schlee W, et al. A review of physical and cognitive interventions in aging. *Neurosci Biobehav Rev*. 2014;44:206–20.





# Assistive Devices, Falls, and Cognitive Aspects

8

Susan W. Hunter

## Introduction

Mobility is fundamental to successful and active aging and is intimately related to health status and quality of life in older adults [1]. Yet, mobility disability is common in adults over the age of 65 years. Approximately 25–33% of community-dwelling older adults specifically report difficulty with the activities of walking and climbing stairs [2].

Participation in rehabilitation can improve functional mobility of older adults through gains in strength, balance and endurance [3]. It is important to note, however, that while these exercise programs may improve balance, people may still have a residual level of balance impairment or unsteadiness in walking related to health problems that are common among older adults (e.g., stroke, osteoarthritis, neuropathy). A first-line rehabilitation strategy in this scenario for balance and gait disorders is provision of a mobility aid (e.g., cane or walker).

Mobility aids, such as canes or walkers, are used to compensate for deficits in balance, coordination, sensation and strength [4]. Research indicates that for people with balance impairment, appropriate use of a gait aid can improve walking stability [4, 5]. There are additional benefits to mobility aid; they are seen to significantly improve the quality of life of older adults by allowing greater ambulation and social participation. The use of mobility aids in community-dwelling older adults is estimated at 24% [6] and among institution-dwelling older adults it is estimated at 70% [1]. This is a serious problem for long-term care facilities as 79% of residents have cognitive impairment, 80% of residents fall each year and gait aids are a factor in 79.5% of falls [7–9]. There is evidence suggesting that across all ages mobility aid use has increased over time. LaPlante et al. [10] found between 1980 and 1990 there

---

S. W. Hunter (✉)

School of Physical Therapy, University of Western Ontario, London, ON, Canada

e-mail: [susan.hunter@uwo.ca](mailto:susan.hunter@uwo.ca)

was a 26% increase in the use of canes, a 57% increase in the use of walkers and a 65% increase in the use of wheelchairs.

It is important to also appreciate that mobility aids elicit strong emotional responses for older adults who are prospective and current users. Specifically, mobility aids are seen to have both positive and negative connotations for older adults. The positive effects include enabling people to safely perform normal and essential activities of daily living. However, negative feelings are associated with personal and social consequences for users, in particular mobility aid use generates feelings of loss [11, 12] and stigma associated with aging and physical decline [13].

---

## Mobility Aid Use and Falls

While mobility aids can compensate for deficits and improve walking function, there is a growing body of literature on the association between use of mobility aids and falls among community- and institution-dwelling older adults. In a large cross-sectional analysis of data from the National Health and Aging Trends Study in the United States ( $n = 7609$  participants), there was no relationship found between the use of mobility aids and reported history of falls in the previous year [6]. In another cross-sectional study by Graafmans et al. [14], high levels of physical activity and use of mobility aid were found to be protective in association to history of falls in the past 12 months. These studies' main objective was the specific evaluation of the relationship between mobility aid use and falls, yet the use of cross-sectional designs in falls research is a major limitation because of the loss of the temporal order between the exposure and the outcome.

To address the previous methodological limitations in cross-sectional studies, the research from large prospective studies has been important in disentangling this relationship between mobility aids and falls. The systematic review and meta-analysis of prospective cohort studies by Deandrea et al. [15] found mobility aid use in community-dwelling older adults was associated with an odds ratio of sustaining any fall at 2.50, 95%CI (1.80, 3.47) and 3.20, 95%CI (1.70, 6.01) for recurrent falls. In this systematic review, mobility aid use was quantified with a simple dichotomous response of yes/no use, so there is no information available about presence of a differential risk by type of aid. The incidence of fall-related injuries associated with use of walkers and canes has been estimated at 130.7 per 100,000 people [16]. Importantly, the injury rates varied with the type of aid, such that walkers were associated with seven times as many injuries as canes. Additionally, injury rates among women exceeded that of men at 2.5 for walkers and 1.4 for canes [16].

While this epidemiologic literature demonstrates an increased risk of falls and fall-related injuries with use of mobility aids in both community- and institution-dwelling populations of older adults, the research does not provide many insights into the mechanisms of these falls. Specifically, did people who were using a mobility aid fall while using their aid or when not using their aid, was the fall a result of unsafe use of the aid or did the aid interfere with limb movement for a



recovery stepping strategy or as the results of poor maintenance of equipment. There is support from video analyses of falls and fall incident reports among older adults living in residential care that mobility aids were a causative factor in 79.5% of falls [9].

There are several possible explanations for the increased falls risk with mobility aid use. It has been observed the gait of older adults who use a mobility aid is more unstable and irregular than that of older adults independently mobile without need for a mobility aid [5]. Importantly, the gait quality is improved when older adults use their mobility aid compared to unassisted walking [5]. Therefore, mobility aid use could be a proxy for the presence of intrinsic functional limitations, such as balance or gait problems, but the elevated risk remains even when those factors have been taken into account [15]. Additional considerations that are not directly related to the need to use an aid but could link mobility aid use to an elevated falls risk include (1) interference with lower extremity movement during balance recovery to a perturbation, (2) it prevents the use of a person's hands to effectively reach for support when there is a loss of balance, (3) it increases the cognitive demands related to attentional processing and neuromotor control leading to an unstable gait [4], (4) unsafe use of the equipment and (5) unsafe maintenance of equipment [17, 18].

There is research that has evaluated the potential of mobility aid use to interfere with limb movements during balance recovery, specifically reaching and grasping of the upper extremity and stepping responses in the lower extremity. The ability to grasp structures for support in reaction to instability is an important hardwired response of the postural repertoire, but this may be compromised if a person is holding an object like a mobility aid. There exists a potential conflict between holding an object that provides support and releasing that object to grasp for another object. Bateni et al. [19] found in healthy young adults while using a single cane the central nervous system gives priority to the ongoing task of holding an object, even when it has no stabilizing value to perturbations that would lead to a fall. Bateni et al. [20] also found that use of a mobility aid significantly interferes with lateral compensatory stepping reactions during a balance perturbation in healthy young adults. Specifically, collisions with the stepping foot and the mobility aid were common; it was present for 60% and 11% of stepping responses with a standard walker and a single cane, respectively. Therefore, there is empirical evidence to support mobility aids impede automatic reactive postural responses to an unexpected perturbation.

Mobility is a complex activity and the ability to move through one's home and community, even during the performance of normal activities of daily living, requires significant cognitive resources for maintaining balance and adapting walking to negotiate obstacles and planning a path [21]. Older adults with dementia have an annual fall risk of 60–80%, twice that of the cognitively normal [22], and have a higher risk of major fall-related injuries, such as hip fractures [23]. In a systematic review and meta-analysis by Hunter et al. [24], the use of any mobility aid by older adults with dementia living in an institutional setting increased falls risk with an odds ratio of 3.6 (1.4, 9.0) and use of a walker was associated with an odds ratio of

2.07 (1.06, 4.4). It is important to note that in this systematic review no studies were found that had evaluated the association of mobility aid use to falls in people with dementia living in the community; thus, this remains an important area for further research considering the majority of people with dementia live in this setting. The cognitive deficits associated with dementia can impact performance during complex motor tasks, impair motor learning and lead to unsafe use of the equipment due to forgetting rules for use.

It is important to appreciate that the majority of older adults using a cane or walker obtain the device without consultation with a health-care professional. Liu et al. found that 67% of cane users [18] and 80% of walker users [17] lacked the involvement of a health-care practitioner to select and provide instruction on the correct use of their mobility aid. Improper fitting of a mobility aid was found for both walker (55%) [17] and cane (54%) [18] users; this can lead to adverse biomechanical consequences on a person's upright posture when using the aid [25]. As a consequence, aids that were too low resulted in a forward leaning posture, found in 40% of mobility aid users in static standing and 50% during ambulation [17]. A forward leaning posture shifts the person's center of gravity close to their limits of stability creating greater likelihood that balance will be lost with perturbations that occur with even normal weight transfer during gait and also in the presence of unexpected perturbations, even of a small magnitude. There is some evidence to support that the underlying balance ability of an individual may need to be taken into consideration when selecting the hand grip height of a 4-wheeled walker, specifically people with poor balance function need to have higher grip height than usual recommendations [25]. Improper technique was also common among cane users (31%); specific problems identified were use of a cane on the incorrect side and inability to appropriately sequence the cane and contralateral leg [18]. Also, all people in the two studies by Liu et al. reported their mobility aids or their use of the equipment had not been checked by a health-care professional since they had obtained the device [17, 18]. This information highlights an area that should be a regular topic of review in fall prevention practices.

Maintenance of equipment is also an important consideration for safety of older adults using mobility aids. A person may have appropriate fitting and training in the use of a mobility aid, but if the equipment is not properly maintained then failure of the equipment can lead to falls. Liu et al. found that improper maintenance was common for both cane (19%) [18] and walker users (18%) [17]. Specific areas of equipment problems included worn out or loose rubber tips on canes and for walkers, loose handgrips and brakes that were too loose. Regular maintenance of the equipment should be actively promoted for all users of mobility aids.

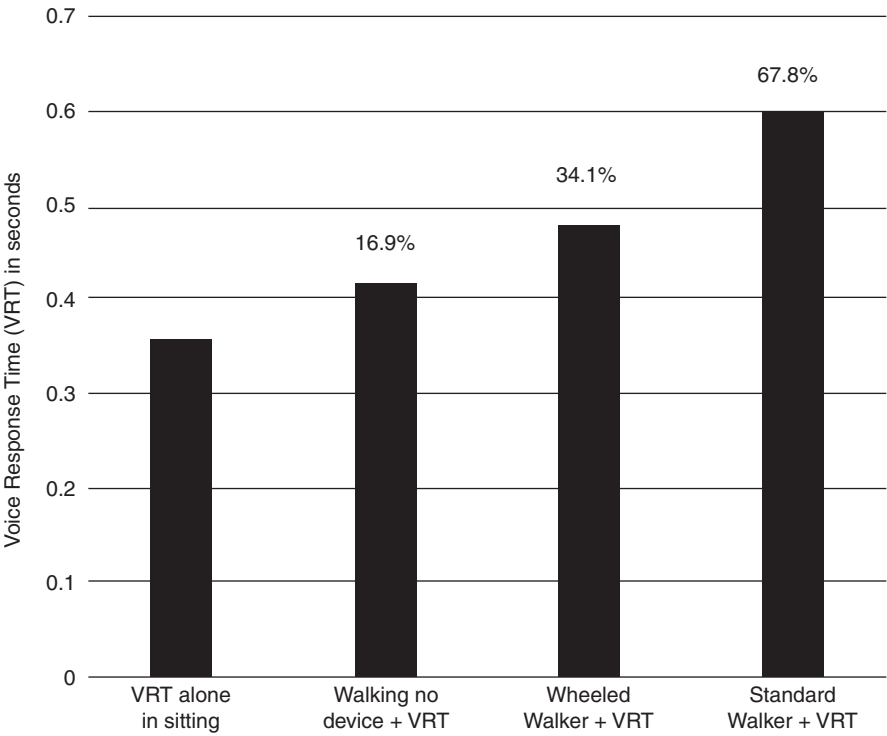
As the previous paragraphs have outlined, there are several mechanisms by which mobility aid use can increase the risk of falls in older adults. In order to be able to reduce the risk of falls associated with their use, an understanding of these factors by health-care practitioners that increase or decrease falls risk is needed in order to deliver assessments to identify deficits and then provide targeted interventions for older adults.

## Mobility Aid Use and Cognitive Aspects

Gait and balance are complex tasks involving the integration of information from multiple systems to maintain postural stability. Cognition, specifically executive function, plays a key role in the normal regulation of walking and balance [26]. Executive function, which comprises the set of cognitive processes that use sensory information to modulate behavior, is required for planning movements, dividing attention and responding to changes in the environment [27, 28]. Complex tasks need high levels of motor control and require cognitive function to generate motor patterns that are responsive to multiple sensory inputs and environmental conditions [29, 30]. Impairment in executive function is associated with an increased falls risk [31].

Observing people during a gait task while they simultaneously perform another task—the dual-task paradigm—is a well-recognized way to assess the interaction between cognition and mobility and reflects circumstances that lead to falls in real life [26, 29]. The brain has limited cognitive processing resources for performance of multiple simultaneous tasks [32]. Each task is assumed to require a proportion of that limited resource and the more complex the task, the greater the processing capacity demands will be. Performance of multiple tasks at the same time would also require a summed demand on the processing capacity. If the demands of doing a single complex task or multiple tasks simultaneously exceed the cognitive capacity of an individual, then performance on one or all tasks will deteriorate by creating cognitive-motor interference [29, 33]. The magnitude of the cognitive-motor interference is referred to as the cognitive load, or the difference between the single and combined tasks, and quantifies the demands on executive function resources.

Wright et al. [34] were the first to evaluate the cognitive demands of using a mobility aid; their study population were healthy young adults ( $n = 10$ , average age =  $30.8 \pm 8.1$  years) who did not use any aid. Their concern was that people newly learning to use a mobility aid would require greater cognitive resources to appropriately use the equipment. Consequently, if the demands challenge the cognitive capacity of the individual large enough then this could compromise stability. Wright et al. [34] utilized dual-task paradigm methodology in the study, evaluating people during the following tasks of walking with a standard walker and a 4-wheeled walker, performing a voice response time (VRT) task singly in sitting (task was to make a vocal response as rapidly as possible to the presentation of a 1500 Hz sound, the delay between presentation of the signal and the vocal response was measured in seconds) and then combining the two activities together. The VRT was longest when walking with a standard walker, followed by walking with the 4-wheeled walker, walking with no assistive device and finally performing the vocal response task only (see Fig. 8.1). The VRT while walking with the standard walker was significantly different from all the other test conditions. Using the data presented in the paper, the cognitive load for walking with the wheeled walker and VRT was  $-14.74 \pm 15.17\%$  and walking with standard walker and VRT was  $-143.16 \pm 32.80\%$  compared to walking with no aids. The negative value of the cognitive load indicates that performance worsened in the dual-task condition.



**Fig. 8.1** Mean voice response times (VRT) in seconds for single-task VRT and dual-task gait testing for young adults ( $n = 10$  subjects) and dual-task costs. (Figure is modified from Wright and Kemp [34])

Wellmon et al. [35] evaluated VRT in older adults ( $n = 105$ , average age =  $84.1 \pm 5.6$  years) who were independently ambulatory with either a 4-wheeled walker, a single straight cane or used no mobility aid. The VRT task was similar to that described for Wright et al. [34] and was measured in the subjects while standing still and while walking with their mobility aid. VRTs were not different between the three groups when evaluated in standing, but during walking, the VRT for the 4-wheeled walker group (726.30 msec) was significantly longer than the group with no aids (563.60 msec). The gait velocity also slowed down from usual gait with the mobility aid to during the dual-task assessment: for no mobility aid users ( $1.35 \pm 0.49$  to  $1.35 \pm 0.54$ ), for single straight cane users ( $0.90 \pm 0.45$  m/sec to  $0.87 \pm 0.42$  m/sec) and for 4-wheeled walker users ( $0.83 \pm 0.27$  m/sec to  $0.80 \pm 0.27$  m/sec).

The study by Wellmon et al. [35] highlights the potential trade-offs in performance that can occur on each of the two tasks when they are performed simultaneously. Earlier we highlighted that performance can change in one or both tasks, but most research in gait dual-task testing in general has focused on performance changes in gait without detailing changes in the secondary task between single- and dual-task conditions. Using data from the Wellmon et al. [36] manuscript, the

cognitive load for change in gait velocity was 0%, -3.3% and -3.6% (no aid, straight cane, 4-wheeled walker) and the cognitive load for the VRT was -9.45%, -13.62% and -27.9% (no aid, straight cane, 4-wheeled walker). This pattern would be classified as motor-related cognitive interference (motor performance remains stable while cognitive performance deteriorates). In the presence of competing demands that exceed cognitive capacity, the preservation of the mobility task to optimize postural stability at the expense of the secondary task is called the posture first strategy [37]. A posture second strategy, the preservation of the secondary cognitive task performance at the expense of a deterioration in the gait task, is associated with an increased falls risk [26]. This is an area that has received limited evaluation in the literature on dual-task effects with use of mobility aids, yet should have greater prominence.

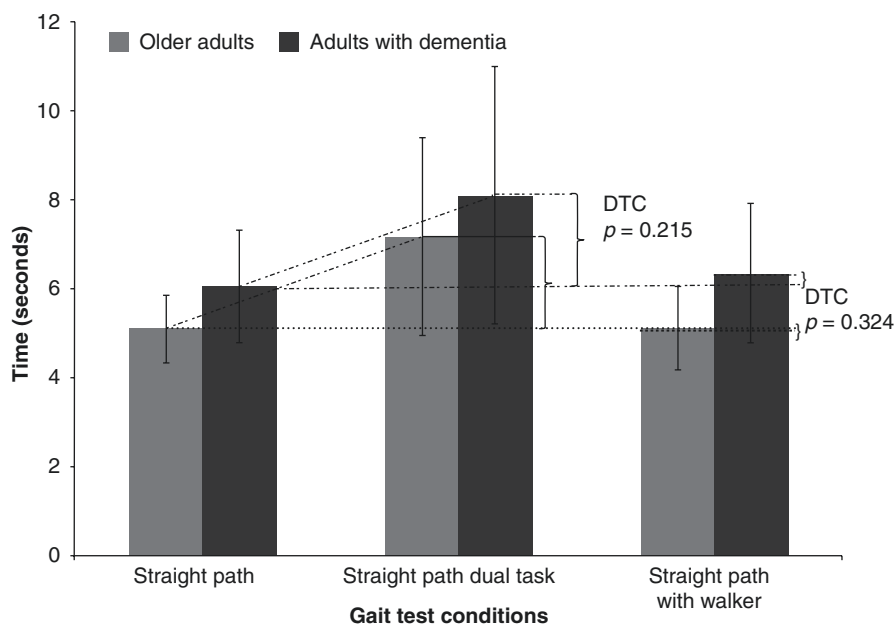
Miyasike-daSilva et al. [38] found that the use of mobility aids reduced cognitive load during dual-task gait testing in the presence of situations that challenge postural stability. The study investigated the effect of 4-wheeled walker use on walking performance and attentional demand under a challenging walking condition using dual-task gait testing with voice reaction time as the secondary activity. Young healthy participants walked in a straight path on flat level ground or along a balance beam (5 cm high and 5 cm wide). Slower VRTs, reduced gait speed, and increased number of missteps (>92% of all missteps) were observed during beam walking. During dual-task testing without use of the walker, there was no influence on performance during level walking. Walker use reduced attentional demand while walking on the beam, but did not impact performance demands on the level. Not surprisingly, increasing the base of support with use of the walker while walking on the beam (e.g., the walker straddled the beam) lead to a reduction in cognitive demand. There is little ecological validity to this study to normal use of a 4-wheeled walker. Research evaluating the effect of walker use during dual-task testing conditions in people with compromised dynamic postural stability would be of interest.

Mobility aid use increases the cognitive demands on the user, regardless of cognitive health, suggesting that executive function is necessary for their proper use. Importantly, distractions within the environment (e.g., noise, other people, participating in a conversation) could add to the cognitive demands. An unappreciated source of additional demands on cognitive abilities for mobility aid use include demands of strategy use (e.g., understanding and recalling why, when, where and how to use a strategy, such as putting on the brakes with the mobility aid). It is important to now consider the effects of mobility aid use in people with cognitive impairment and dementia. Importantly, the provision of a mobility aid to people with dementia may occur at a point in the disease process when brain function is challenged and available cognitive resources are limited. Therefore, contrary to the intended benefits, people with dementia may experience instability, falls and fractures while using a mobility aid in excess to that experienced by cognitively healthy adults.

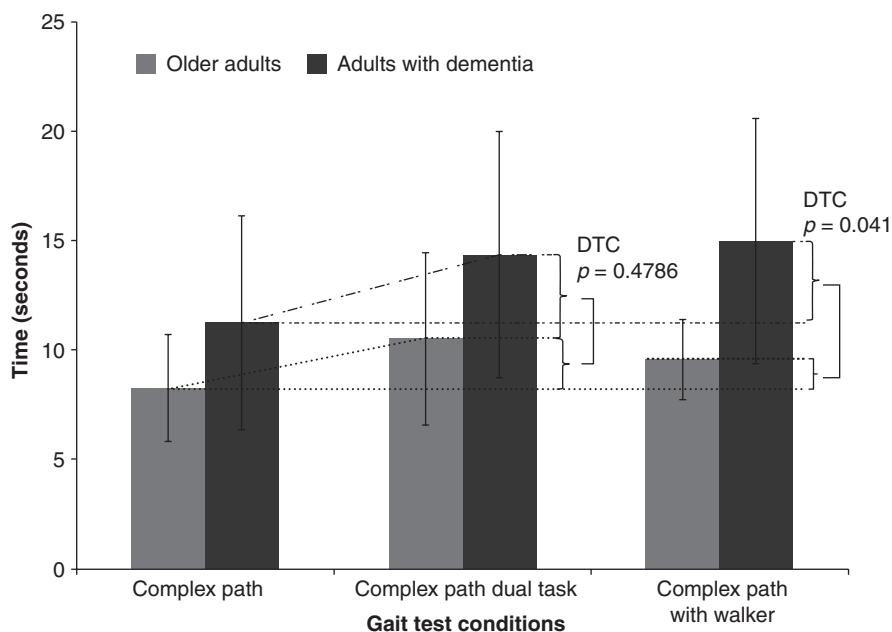
Gait and mobility impairments are common in adults with dementia [39] and the essential relationship between cognitive function and postural stability is most evident when gait performance is challenged under dual-task testing with the addition of an extra cognitive load. Hunter et al. [40] were able to demonstrate that gait

performance is adversely affected in people with cognitive impairment, specifically mild cognitive impairment and mild Alzheimer's disease, compared to cognitively healthy older adults during dual-task gait testing. Mobility aids are seen to significantly improve the quality of life of older adults by allowing greater ambulation and social participation. Enhanced physical activity in people with dementia has the benefits of improved physical and cognitive performance, and social engagement [41].

Hunter et al. [40] evaluated the effect of newly learning to use a 4-wheeled walker in people with mild to moderate Alzheimer's disease (AD) ( $n = 14$ , average age =  $72.6 \pm 9.9$  years) who did not have need to use the equipment compared to age- and sex-matched healthy controls ( $n = 14$ , average age =  $72.9 \pm 9.5$  years). An additional feature of this study was the assessment of the path configuration on cognitive load with and without the use of the 4-wheeled walker. The configuration of the walking pattern is relevant in the evaluation of functional abilities. Gait performance under a straight path condition is considered a low cognitive challenge activity while curved or complex path walking is more demanding and can provide meaningful information about daily life walking ability, including adaptation of walking patterns to negotiate obstacles, change directions or plan a path [21]. Ambulation with the walker in a straight path produced a low cognitive load that was not different between the two groups, slightly longer time to complete the task using the 4-wheeled walker (Fig. 8.2). Ambulation with the 4-wheeled walker in the



**Fig. 8.2** Time to complete walking tests for older adults with Alzheimer's disease and healthy older adults under single- and dual-task conditions of using a wheeled walker in a straight path walking pattern. (DTC, dual task cost). (Graph generated from data in Muir-Hunter and Montero Odasso [40])



**Fig. 8.3** Time to complete walking tests for older adults with Alzheimer’s disease and healthy older adults under single- and dual-task conditions of using a wheeled walker in a complex path walking pattern. (DTC, dual task cost). (Graph generated from data in Muir-Hunter and Montero Odasso [40])

complex path produced a significantly different cognitive load in the group with AD at  $-38.1 \pm 23.5\%$  compared to  $-19.7 \pm 21.4\%$  ( $p = 0.041$ ) (Fig. 8.3). Regression modelling identified that lower scores on executive function were associated with longer times across gait testing conditions. Ambulation with a 4-wheeled walker, in particular maneuvering around obstacles, required the greatest attentional cost in the people with dementia.

## Future Directions

While this preceding review draws our attention to several mechanisms by which mobility aid use is associated with falls, the most interesting is the role of cognitive resources to use the equipment. Some of the other identified factors that link to falls are potentially modifiable and should be addressed as part of regular falls risk assessment and intervention strategies. As an emerging area of falls research interest, there is need for studies to continue to expand our understanding of falls mechanisms particularly in older adults with dementia. Therefore, specific evidence informed recommendations for falls prevention is limited at this time and will develop with further research in the area.



## References

- Clarke P, Chan P, Santaguida PL, Colantonio A. The use of mobility devices among institutionalized older adults. *J Aging Health*. 2009;21(4):611–26. <https://doi.org/10.1177/0898264309333313>.
- Shumway-Cook A, Ciol MA, Yorkston KM, Hoffman JM, Chan L. Mobility limitations in the Medicare population: prevalence and sociodemographic and clinical correlates. *J Am Geriatr Soc*. 2005;53(7):1217–21. <https://doi.org/10.1111/j.1532-5415.2005.53372.x>.
- Handoll H, Cameron I, Mak I, Finnegan T. Multidisciplinary rehabilitation for older people with hip fractures. *Cochrane Database Syst Rev*. 2009;(4):CD007125. <https://doi.org/10.1002/14651858.CD007125.pub2>.
- Batani H, Maki BE. Assistive devices for balance and mobility: benefits, demands, and adverse consequences. *Arch Phys Med Rehabil*. 2005;86(1):134–45. <https://doi.org/10.1016/j.apmr.2004.04.023>.
- Härdi I, Bridenbaugh SA, Gschwind YJ, Kressig RW. The effect of three different types of walking aids on spatiotemporal gait parameters in community-dwelling older adults. *Aging Clin Exp Res*. 2014;26(2):221–8. <https://doi.org/10.1007/s40520-014-0204-4>.
- Gell NM, Wallace RB, Lacroix AZ, Mroz TM, Patel KV. Mobility device use in older adults and incidence of falls and health and aging trends study. *J Am Geriatr Soc*. 2015;63(5):853–9. <https://doi.org/10.1111/jgs.13393>.
- Rubenstein LZ, Josephson K, Robbins A. Falls in the nursing home. *Ann Intern Med*. 1994;121(6):442–51.
- Cameron ID, Murray GR, Gillespie LD, et al. Interventions for preventing falls in older people in nursing care facilities and hospitals. *Cochrane Database Syst Rev*. 2010;(1):CD005465. <https://doi.org/10.1002/14651858.CD005465.pub2>.
- Robinovitch SN, Feldman F, Yang Y, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet*. 2013;381(9860):47–54. [https://doi.org/10.1016/S0140-6736\(12\)61263-X](https://doi.org/10.1016/S0140-6736(12)61263-X).
- LaPlante M, Hendershot G, Moss A. Assistive technology devices and home accessibility features: prevalence, payment, need and trend. *Adv Data*. 1992;217:1–11.
- Aminzadeh F, Edwards N. Exploring Seniors' views on the use of assistive devices in fall prevention. *Public Health Nurs*. 1998;15(4):297–304. <https://doi.org/10.1111/j.1525-1446.1998.tb00353.x>.
- Gitlin L, Schemm R, Landsberg L, Burgh D. Factors predicting assistive device use in the home by older people following rehabilitation. *J Aging Health*. 1996;8(4):554–75.
- Resnik L, Allen S, Isenstadt D, Wasserman M, Iezzoni L. Perspectives on use of mobility aids in a diverse population of seniors: implications for intervention. *Disabil Health J*. 2010;2(2):77–85. <https://doi.org/10.1016/j.dhjo.2008.12.002.Perspectives>.
- Graafmans WC, Lips P, Wijlhuizen GJ, et al. Daily physical activity and the use of a walking aid in relation to falls in elderly people in a residential care setting. *Z Gerontol Geriatr*. 2003;36(1):23–8. <https://doi.org/10.1007/s00391-003-0143-8>.
- Deandrea S, Lucenteforte E, Bravi FF, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology*. 2010;21(5):658–68. <https://doi.org/10.1097/EDE.0b013e3181e89905>.
- Stevens JA, Thomas K, Teh L, Greenspan AI. Unintentional fall injuries associated with walkers and canes in older adults treated in U.S. emergency departments. *J Am Geriatr Soc*. 2009;57(8):1464–9. <https://doi.org/10.1111/j.1532-5415.2009.02365.x>.
- Liu H. Assessment of rolling walkers used by older adults in senior-living communities. *Geriatr Gerontol Int*. 2009;9(2):124–30. <https://doi.org/10.1111/j.1447-0594.2008.00497.x>.
- Liu H (Howe), Eaves J, Wang W, Womack J, Bullock P. Assessment of canes used by older adults in senior living communities. *Arch Gerontol Geriatr*. 2011;52(3):299–303. <https://doi.org/10.1016/j.archger.2010.04.003>.



19. Bateni H, Zecevic A, McIlroy WE, Maki BE. Resolving conflicts in task demands during balance recovery: does holding an object inhibit compensatory grasping? *Exp Brain Res.* 2004;157(1):49–58. <https://doi.org/10.1007/s00221-003-1815-8>.
20. Bateni H, Heung E, Zettel J, McIlroy WE, Maki BE. Can use of walkers or canes impede lateral compensatory stepping movements? *Gait Posture.* 2004;20(1):74–83. [https://doi.org/10.1016/S0966-6362\(03\)00098-5](https://doi.org/10.1016/S0966-6362(03)00098-5).
21. Lowry KA, Brach JS, Nebes RD, Studenski SA, VanSwearingen JM. Contributions of cognitive function to straight- and curved-path walking in older adults. *Arch Phys Med Rehabil.* 2012;93(5):802–7. <https://doi.org/10.1016/j.apmr.2011.12.007>.
22. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med.* 1988;319(26):1701–7.
23. Asada T, Kariya T, Kinoshita T, et al. Predictors of fall-related injuries among community-dwelling elderly people with dementia. *Age Ageing.* 1996;25(1):22–8. <http://www.ncbi.nlm.nih.gov/pubmed/8670525>.
24. Fernando E, Fraser M, Hendriksen J, Kim C, Hunter S. Risk factors for falls in people with dementia: a systematic review. *Physiother Can.* 2016;69(2):161–70. <https://doi.org/10.3138/ptc.2016-14>.
25. Choi HJ, Ko CY, Kang S, Ryu J, Mun M, Jeon HS. Effects of balance ability and handgrip height on kinematics of the gait, torso, and pelvis in elderly women using a four-wheeled walker. *Geriatr Gerontol Int.* 2015;15(2):182–8. <https://doi.org/10.1111/ggi.12246>.
26. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23(3):329–42. <https://doi.org/10.1002/mds.21720>.
27. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord.* 2006;21(7):950–7. <https://doi.org/10.1002/mds.20848>.
28. Horak FB. Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing.* 2006;35(SUPPL.2):7–11. <https://doi.org/10.1093/ageing/af077>.
29. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture.* 2002;16(1):1–14. [https://doi.org/10.1016/S0966-6362\(01\)00156-4](https://doi.org/10.1016/S0966-6362(01)00156-4).
30. Snijders AH, van de Warrenburg BP, Giladi N, Bloem BR. Neurological gait disorders in elderly people: clinical approach and classification. *Lancet Neurol.* 2007;6(1):63–74. [http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17166803&retmode=ref&cmd=prlinks%5Cnpapers3://publication/doi/10.1016/S1474-4422\(06\)70678-0](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=17166803&retmode=ref&cmd=prlinks%5Cnpapers3://publication/doi/10.1016/S1474-4422(06)70678-0).
31. Muir S, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing.* 2012;41(3):299–308. <https://doi.org/10.1093/ageing/afs012>.
32. Plummer P, Eskes G. Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front Hum Neurosci.* 2015;9(April):225. <https://doi.org/10.3389/fnhum.2015.00225>.
33. Muir-Hunter SW, Wittwer JE. Dual-task testing to predict falls in community-dwelling older adults: a systematic review. *Physiotherapy.* 2015;102(1):29–40. <https://doi.org/10.1016/j.physio.2015.04.011>.
34. Wright DL, Kemp TL. The dual-task methodology and assessing the attentional demands of ambulation with walking devices. *Phys Ther.* 1992;72(4):306–12. discussion 313–315.
35. Wellmon R, Pezzillo K, Eichhorn G, Lockhart W, Morris J. Changes in dual-task voice reaction time among elders who use assistive devices. *J Geriatr Phys Ther.* 2006;29(2):74–80. <https://doi.org/10.1519/00139143-200608000-00006>.
36. Wellmon R. Does the attentional demands of walking differ for older men and women living independently in the community? *J Geriatr Phys Ther.* 2012;35(2):55–61. <https://doi.org/10.1519/JPT.0b013e31822ad40b>.

37. Shumway-Cook A, Woollacott M. Attentional demands and postural control: the effect of sensory context. *J Gerontol A Biol Sci Med Sci*. 2000;55(1):M10–6. <https://doi.org/10.1093/gerona/55.1.M10>.
38. Miyasike-daSilva V, Tung JY, Zabukovec JR, McIlroy WE. Use of mobility aids reduces attentional demand in challenging walking conditions. *Gait Posture*. 2013;37(2):287–9. <https://doi.org/10.1016/j.gaitpost.2012.06.026>.
39. Allan LM, Ballard CG, Burn DJ, Kenny RA. Prevalence and severity of gait disorders in Alzheimer's and Non-Alzheimer's dementias. *J Am Geriatr Soc*. 2005;53(10):1681–7. <https://doi.org/10.1111/j.1532-5415.2005.53552.x>.
40. Muir-Hunter S, Montero-Odasso M, Montero Odasso M. The attentional demands of ambulating with an assistive device in older adults with Alzheimer's disease. *Gait Posture*. 2017;54(3):202–8. <https://doi.org/10.1016/j.gaitpost.2017.03.011>.
41. Ardern CI, Rotondi M. Knowledge synthesis report: the role of physical activity in the prevention and management of Alzheimer's disease — implications for Ontario. Ontario Brain Inst. 2013.



# Medication Use and Falls in People with Cognitive Impairment. Assessment and Management Strategies

Allen R. Huang and Louise Mallet

## Introduction

The world population is living longer. Life expectancy has increased globally to 70.8 years in 2010–2015, and the fastest growing portion of the population is those people older than 60 years [1]. Change in the way we communicate about aging issues is being catalyzed by organizations such as the Frameworks Institute ([www.frameworksinstitute.org](http://www.frameworksinstitute.org)). For example instead of the use of catastrophic terms such as the “grey tsunami” or “rising tide of elderly people” we can reframe statements using more positive language like “As [we] live longer and healthier lives...” [2]. Likewise, the language describing medication use in older people needs to be refreshed. The term polypharmacy is continually evolving. The number of different medications an older person regularly takes will likely continue to increase due to the discovery of new therapeutic agents. Rather than limit the focus on just the number of different medications, the concept of appropriate pharmacotherapy should be used. There is no consistent definition at which number of active medications one attains the label “polypharmacy.” A systematic review of the definition of polypharmacy reported a range of greater than 2 to more than 10 [3]. This review also highlighted other terms associated with medication use including “major,” “hyper,” “excessive,” “persistent,” and “chronic” polypharmacy. The adjectives “appropriate” and “inappropriate” have also been attached to the polypharmacy construct. Is the number of active medications no longer meaningful [4]? It is time to flip the terms we use associated with

---

A. R. Huang (✉)

Division of Geriatric Medicine, Department of Medicine, University of Ottawa & The Ottawa Hospital, Ottawa, ON, Canada  
e-mail: [allenhuang@toh.ca](mailto:allenhuang@toh.ca)

L. Mallet

Faculty of Pharmacy, Université de Montréal, and Clinical Pharmacist in Geriatrics, McGill University Health Centre, Montreal, QC, Canada  
e-mail: [louise.mallet@umontreal.ca](mailto:louise.mallet@umontreal.ca)

medication use to a positive light. Using medications effectively, whether to limit disease progression, treat symptoms or improve function with its attendant improvements in quality of life is the goal of therapeutics and should not depend on the age of the person. A Cochrane systematic review also summarized the state of best practice in attempting to achieve appropriate prescribing [5]. The ultimate outcome and observable sign of success for changing our terms for medication use would be the future obsolescence and disappearance of the concept of “de-prescribing”!

---

## Effects of Medications in Older People: What Is Different?

### Patient Factors

#### Pharmacokinetic Changes

With aging, pharmacokinetic changes are observed in terms of drug absorption, distribution, metabolism and excretion which can lead to possible adverse drug events (ADEs) if prescribing is not modified [6]. Table 9.1 lists the changes in the pharmacokinetics of drugs with normal aging and in frail older patients. Additional factors such as the presence of multiple co-morbidities, altered homeostasis, drug interactions, decreases in renal function and an increase in the number of medications may also contribute to drug-related problems.

#### Absorption

Drug absorption, in general, remains relatively stable in the older patient. A delay in the rate of the drug absorption may be observed with no significant impact on the overall absorption. Absorption of oral medications may be affected by changes in the aging gut such as an increase in gastric pH due to hypochlorhydria, a reduction in gut motility, slowed gastric emptying, decreased gastric surface area and decreased gastrointestinal blood flow [7, 8]. Drugs which require an acidic environment for optimal absorption, such as calcium carbonate and ketoconazole [9], may be affected by the concurrent use of a proton pump inhibitor, a drug which is widely used, frequently with unclear indications. Absorption of medications by the subcutaneous, intramuscular and transdermal routes can be altered in frail older patients with decreased muscle mass [10, 11]. Crushing pills to improve drug ingestion is common and yet no studies have been done to determine the effect on drug absorption. Supplemental calcium, if co-administered, will chelate with certain drugs, for example, quinolone antibiotics and levothyroxine, decreasing their absorption and their efficacy [11, 12]. Decompensated congestive heart failure can decrease blood flow to the gastrointestinal tract with a decrease in the absorption of some drugs. For example, oral absorption of furosemide can be impaired due to slow gastric emptying and can contribute to furosemide resistance in decompensated heart failure [11].

#### Distribution

The body composition changes that occur with aging involve an increase in total body fat of 18–36% along with a decrease in lean body mass. These changes result

**Table 9.1** Changes in pharmacokinetics with normal aging and in frail older patients

	Age-related changes	Clinical impact	Frail elderly
Absorption	No significant changes	No clinical impact	↓↓
Distribution	↑ Body fat	↑ volume of distribution for liposoluble drugs Adjust dosage for drugs such as anti-psychotics, anti-depressants, benzodiazepines	↑↑
	↓ Total water	↓ volume of distribution of water-soluble drugs Adjust dosage for drugs such as digoxin, lithium, diuretics	↓↓
	↓ Albumin	↑ free fraction of drugs for drugs >90% bound to albumin such as phenytoin, valproic acid, sertraline, warfarin	↓↓
Metabolism	↓ Hepatic blood flow	↓ first-pass extraction by the liver such as metoprolol, morphine and verapamil	↓↓
	↓ Phase I metabolism	↓ metabolism of oxidation reaction	↓
	Esterase enzymes	↓ metabolism of drugs metabolized by esterase enzymes. Decreased conversion of pro-drug enalapril to enalaprilat	↓↓
	↓ Phase II metabolism	No changes with normal aging	↓↓ Changes in glucuronidation of acetaminophen and clearance of metoclopramide by sulfation
Elimination	↓ Glomerular filtration rate	↓ elimination of drugs excreted renally such as ciprofloxacin, digoxin, pregabalin	↓↓
	↓ tubular secretion	↓ elimination of drugs excreted via tubular secretion such as cimetidine, trimethoprim	↓↓
	Serum creatinine	With normal aging, no change in serum creatinine	↓↓ For low weight patient, with no muscle mass, decrease in serum creatinine level

Adapted from Mallet [11]

in an increase in the half-life of lipophilic medications such as long-acting benzodiazepines, anti-psychotics, and anti-depressants and can result in prolonged effects and ADEs in older patients [11]. Older people who have low body weight, decreased muscle mass and increased body fat are at greater risk of presenting with serious adverse effects or drug toxicities. Medication doses should be adjusted to compensate for these changes.

Total body water decreases by 10–15% with aging. Older people are also at higher risk of developing dehydration during heat waves. Dosing of water-soluble drugs such as digoxin, lithium, oral hypoglycemic agents, and diuretics [11] should be decreased, their effects carefully monitored or discontinued to avoid potential toxicity.

Decreases in serum albumin concentration can be found in the frail or malnourished older individual or accompanying certain chronic disease states [11]. Drugs which are highly bound to albumin (more than 90%), such as phenytoin, warfarin, sertraline, valproic acid, or non-steroidal anti-inflammatory drugs, can increase their free (unbound) drug concentration in this state and result in toxicity. Serum albumin concentration can help prescribers adjust dosages for highly protein-bound drugs [11].

## Metabolism

A decrease of up to 40% in liver volume and a decrease in hepatic blood flow has been described with aging [11]. Hepatic clearance of drugs with a significant first-pass extraction ratio, such as metoprolol, morphine and verapamil, can be affected with a resultant increase in drug plasma level [11]. Studies have reported the effect of frailty on the activity of enzymes involved in the metabolism of some drugs. Phase I reactions (oxidation, reduction, or hydrolysis) are decreased with aging. Esterases, enzymes involved in phase I oxidative metabolism of different drugs, have been associated with decreased activity with aging. For example, the decreased activation of a pro-drug such as enalapril to its active metabolite enalaprilat via hepatic esterases has been documented. Other drugs such as amitriptyline, citalopram, sertraline and venlafaxine undergo a decrease in phase I metabolism (oxidation and reduction) and dosage should be adjusted accordingly.

Studies have also reported pharmacokinetic modifications in phase II metabolism in frail older people for metoclopramide and paracetamol [13, 14]. Glucuronidation of paracetamol and clearance of metoclopramide by sulfation have also been shown to be considerably reduced [13, 14].

## Elimination

The reduction in muscle mass of an older person, which results in a decrease in creatinine production, can offset the increase in serum creatinine concentration due to the decline in kidney mass, renal blood flow, glomerular filtration rate and tubular secretion rate, resulting in a normal value of serum creatinine concentration [11]. Creatinine clearance estimation using the Cockcroft and Gault equation is commonly used to help clinicians adjust dosage for renally excreted drugs [11]. However, a specific formula to estimate creatinine clearance in frail older patients with low muscle mass and low serum creatinine concentration does not yet exist. In these

types of patients, estimation of creatinine clearance using the “non-adjusted” serum creatinine will often overestimate the true value. For example, using the Cockcroft and Gault equation to estimate creatinine clearance for a 90-year-old woman, who weighs 38 kg, with a serum creatinine concentration of 45  $\mu\text{mol/L}$ , will result in an overestimated value of 44 mL/min. When this value of 44 mL/min is used to adjust the dose of renally excreted medications, side effects are often reported. “Adjusting” the serum creatinine by substituting a “normal” value of 70  $\mu\text{mol/L}$  in the case above results in a decreased estimated creatinine clearance of 28 mL/min. Clinical judgement and additional corrections should be considered when dosing renally excreted medications in these patients [11].

### Pharmacodynamic Changes

Pharmacodynamic changes include affinity and number of target receptors, drug concentration at the receptor sites, and alterations in homeostatic mechanisms. Changes in the permeability of the blood-brain barrier with aging have been reported which can increase the sensitivity to central nervous system drugs. Older people can therefore be more sensitive to the effects of benzodiazepines and drugs with anticholinergic properties. These drugs should be avoided.

Older people have blunted baroreceptor reflexes and responses, which places them at higher risk for postural hypotension. With the cardiovascular system, a decline in the responsiveness of beta-receptor activity may be observed with both beta-agonists and beta-blockers. Studies have shown that older people have a lower reduction in blood pressure from beta-blockers [15].

### Cognitive Impairment

Deficits in working memory and executive function are factors which will contribute in medication non-adherence in older patients with complex medication regimens [16]. Medication adherence requires adequate cognitive skills to successfully complete tasks such as getting medications from the pharmacy, remembering to refill medications, understanding and following directions, using a medication dispensing device such as pill boxes, blister packs, Dispill™ or dosette box, and organizing doctor follow-up appointments.

In a scoping review on medication adherence in older patients with cognitive impairment or dementia, Hudani reported a prevalence of non-adherence of 2–59%. Barriers to adherence were cognitive impairment, poor communication with prescribers, lack of social support, and increased pill burden. Some interventions considered to improve adherence included alternate dosage forms and the use of multi-compartment pillboxes [17].

A systematic review by Campbell et al. was done to identify barriers to medication adherence in cognitively impaired older adults and interventions to improve that situation. Barriers to adherence included understanding new directions, living alone in the community, factors related to patient-caregiver relationship such as the concerns for recognizing emergency situations, administration concerns for agitated patients, caregiver burden and scheduling logistics within care routines. The authors concluded that frequent human communication as reminder systems are more likely to improve adherence than non-human reminders [18].

## **Prescriber Factors**

### **Potentially Inappropriate Medications (PIMs)**

#### **Beers' Criteria**

Beers' criteria, named after the American geriatrician Dr. Mark Beers, was initially published in 1991 and provided a list of drugs to avoid using in the U.S. elderly nursing home population. His criteria were revised and updated in 1997 and in 2003 to include all geriatric care settings such as primary care, outpatient and hospitalized inpatients. The American Geriatrics Society subsequently assumed responsibility for future updates, which were published in 2012, 2015, and 2019 [19]. The Beers Criteria are evidence based and include medications listed in different categories to be avoided in older patients such as drugs in certain diseases, drug-drug interactions, dosage adjustment for decreased renal function, and drugs with anti-cholinergic properties. The use of inappropriate medications in older people has been associated with ADEs and increased health care costs [20]. The Beers Criteria have been used as a quality of care measure in different settings. This list is not a substitute for clinical judgement.

#### **STOPP and START Criteria**

STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment) criteria were developed using a Delphi consensus methodology in 2006 in Ireland to address the limitations in the Beers criteria [21]. This list, updated in 2015 [22], has been validated in a number of geriatric settings: acute hospital, primary care and nursing homes. STOPP/START criteria can help guide better medication use and should not replace clinical judgement.

A systematic review on the prevalence of PIMs in older adults was published in 2013 [23]. The authors reported that the STOPP/START criteria appear to be more sensitive than the 2002 version of the Beers criteria. However, when looking at the clinical and economic impact of the STOPP/START criteria, limited evidence was detected. In two observational studies, a potential association between the identification of PIM by STOPP criteria and potentially avoidable ADEs were detected, the extent of which needs to be further studied [23].

#### **STOPPFRAIL Criteria**

A new list of 27 explicit criteria for PIMs prescribed in frail older adults with limited life expectancy has been recently published. This list may help physicians and pharmacists in considering stopping medications in these types of patients in any health care setting. This list will need to be validated in clinical studies [24].



**Table 9.2** Example of common prescribing cascades

Drug 1	Side effect	Addition of drug 2
Amlodipine	Leg edema	Furosemide
Atorvastatin	Leg cramp	Quinine
Ciprofloxacin	Hallucinations	Risperidone
Citalopram	Nausea	Domperidone
Digoxin	Nausea	Metoclopramide
Donepezil	Urinary incontinence	Oxybutynin
Enalapril	Cough	Codeine
Pregabalin	Ankle edema	Furosemide

**Prescribing Cascades**

A prescribing cascade can be defined as a side effect of a medication that is misinterpreted as a new medical condition which triggers the prescription of another medication. This concept was first described in 1997 by Rochon and Gurwitz [25] and the definition updated in 2017 to include subsequent medical device or subsequent over-the-counter drug therapy [26].

Prescription cascades are often detected in clinical practice but rarely reported in the literature. Table 9.2 lists examples of common prescribing cascades. Older patients who are taking multiple medications are at higher risk for cascades. Before prescribing a new medication clinicians should question: is the clinical presentation of the patient possibly related to a side effect from a previously prescribed medication? If the answer is yes, this should be addressed instead of prescribing a new medication.

**Why Do Older People Fall More Often?**

Injurious falls among older people are a major health problem with high costs [27]. Fall risk factors have been meticulously reviewed [28] and classified into intrinsic and extrinsic as listed in Table 9.3. The presence of cognitive impairment especially in patients who are regularly taking medications can affect fall risk in several ways. Cognitive impairment can directly affect mobility as described in other chapters in this book. Cognitive impairment can also impact on medication adherence (see above). For example, unintentional overuse of medications with psychotropic or hypotensive side effects can lead to orthostatic hypotension or excess sedation and result in increased fall risk. Similarly, forgetting to take medications which control cardiac rhythm or rate can lead to dysrhythmias with resultant presyncopal or syncopal events. The healthcare system is also a significant contributing factor in that older people commonly visit several different prescribing physicians and may have their medications dispensed from different pharmacies. This situation, in the absence of an integrated electronic information system that informs all clinicians of all information and changes, can lead to unintended errors and drug interactions [29].

**Table 9.3** Fall risk factors

<i>Intrinsic</i>	Odds ratio (95% confidence intervals)
Increasing age	Only in acute care setting: 1.04 (1.01–1.06) for every 5-year increment
Female sex	No effect
History of previous falls	Hospitalized 2.85 (1.14–7.15) Nursing home 3.06 (2.12–4.41)
Balance impairment	1.98 (1.60–2.46)
ADL dependence	2.26 (2.09–2.45)
Medical conditions	Nursing home 2.08 (1.88–2.31)
Parkinson’s disease	1.65 (1.10–2.47)
Cognitive impairment	Hospitalized 1.52 (1.18–1.94)
Stroke, incontinence	No effect
<i>Extrinsic</i>	
Depression	1.46 (1.27–1.67)
Visual impairment	1.6–2.0 range
Home hazards	1.38 (1.03–1.87)
Pain	2.04 (1.75–2.39)
Dizziness	Nursing home 1.52 (1.33–1.74)
Marital status	No effect
Low education	
Confined to bed	
Postural hypotension	

Adapted from Kwan et al. [28]

### Atypical Presentation of Adverse Drug Events in Older People

The clinical presentation of older patients can be bewildering, atypical, vague and frustrating. An inability to easily and rapidly reconcile patient history, physical exam findings and results from lab tests and diagnostic imaging to a single condition can lead to clinician frustration and dissatisfaction with a resultant labelling of a patient’s problem as being related to aging. The late Sir Bernard Isaacs, a leading clinician, thinker, and author of *Geriatric Medicine Principles* had coined the term “geriatric giants” [30, 31], which refers to the main chronic disabilities of old age that impact on physical, mental, and social domains of older people. The geriatric giants are immobility, instability (falls), incontinence, and intellect (cerebral dysfunction) and thoroughly described in Chap. 1 in this book. Sir Isaacs wrote: “many of these conditions, commonly misperceived to be an unavoidable part of old age, can in fact be improved” [31]. They can be the result of multiple causative factors, typically have a chronic course, frequently impact on an individual’s independence and have no simple cure. Sir Isaacs summarized them as: “They do not kill, but they diminish the value of living.” [31] The recent appearance of any of the geriatric giants in an older person must trigger a careful, comprehensive assessment to clarify possible medication effects that are contributing factors. Probing for changes in the performance of basic (feeding, dressing, toileting, walking, bathing/grooming) or instrumental (housekeeping, managing finances, preparing meals, managing medications, shopping, using transport, using a telephone or other communication

device) activities of daily living is equally important as taking the vital signs of any older patient. High among the potential villains are medications with anti-cholinergic properties. The use of common, non-prescription drugs such as diphenhydramine and dimenhydrinate can lead to delirium (intellect), incontinence (urinary retention with overflow), instability (falls from sedation) and immobility (sedation). As described above explicit lists of PIMs [19, 22] have been well-documented and any person taking drugs that appear on these lists deserves a careful medication review. Fall risk-increasing drugs (FRIDs) have also been well-described and include medications that affect blood pressure control and/or have effects on the central nervous system. Medication use and its relation to fall risk are the topics of a book published in 2016 [32]. Table 9.4 summarizes the information on FRIDs. Although the evidence for harm for different types of medications is variable, the message is clear

**Table 9.4** Fall risk-increasing drugs: Classes and concerns

Category	Drug type	Concerns, odds ratio (95% confidence interval)
Medications affecting the central nervous system (CNS)	Anti-depressants	OR 1.68 (1.47–1.91)
	Tricyclic anti-depressants Selective serotonin reuptake inhibitors (SSRI)	Fracture risk and SSRIs OR 1.72 (1.51–1.95)
	Anti-psychotics	Fracture risk First generation OR 1.68 (1.43–1.99) Second generation OR 1.30 (1.14–1.49) Use in dementia behavior control OR 0.89 (0.75–1.05)
	Lithium (non-toxic levels)	Protective fracture risk OR 0.63 (0.43–0.9)
	Anti-epileptics Phenytoin, carbamazepine, phenobarbital	OR 2.6 (1.5–4.4)
	Benzodiazepines Zolpidem, zopiclone, zaleplon, eszopiclone	OR 1.51 (1.09–1.63) OR 1.94 (1.10–3.42)
	Levodopa for Parkinson's disease	Initiation of use OR 4.18 (1.75–10.02) Population cross-section OR 1.67 (1.00–2.78)
	Memantine	No effect OR 0.92 (0.72–1.18)
	Cognitive enhancers Donepezil, rivastigmine, galantamine	Meta-analysis, falls, no effect OR 0.88 (0.74–1.04)
	Skeletal muscle relaxants	AOR 2.20 (1.84–2.63)
	Multiple CNS meds	One drug AOR 1.95 (1.35–2.81) Two or more drugs AOR 2.37 (1.14–4.94)

(continued)

**Table 9.4** (continued)

Category	Drug type	Concerns, odds ratio (95% confidence interval)
Cardiovascular drugs	Thiazides Anti-hypertensive agents	Initiation of thiazide OR 4.28 (1.19–15.42) Any anti-hypertensive agent OR 1.25 (1.15–1.36) Moderate-intensity treatment OR 1.40 (1.03–1.90) High-intensity treatment OR 1.28 (0.98–4.80)
Glucose control	Metformin	Via impact on vitamin B12 deficiency Each 1 g/day increase OR 2.88 (2.25–3.87)
Pain control	Opioids	Use of any opioid OR 1.38 (1.15–1.66) Fracture risk compared to NSAID use OR 4.1 (3.7–4.5)

that an individual risk-benefit consideration often needs to be done before prescribing any of these agents. A novel computer-assisted tool had been developed and studied and shown to be effective in reducing the prescribing of FRIDs in a cohort of community-dwelling older people and decrease their injury risks [33]. The interplay of cognitive impairment and its effects on medication adherence, resulting in unintentional under or over use, can lead to increased falls in these people. A person who mistakenly doubles their anti-hypertensive medication may experience orthostatic hypotension and falls. Likewise, another person who forgets to take their regular diuretic doses may end up in worsening heart failure and fall because of exertional limitation when walking.

### What Are Key Assessment Features?

A reliable approach to managing medication use in older people is to first obtain a complete medication list which includes all non-prescription agents and alcohol use, then conduct a thorough medication review [34]. Look for a recent change in medication (addition, dose change or discontinuation) or change in the person’s clinical status that may result in changes to drug pharmacokinetics. Identify potential candidates for medication deprescribing [35]. Screening and assessing for cognitive impairment is paramount. There are many tools available, of which the Mini-Mental State Exam [36], Montreal Cognitive Assessment [37], Mini-Cog [38], and the Rowland Universal Dementia Assessment Scale [39] are some examples. If an abnormal result is obtained on cognitive screening, more detailed cognitive assessments and the impact of impairment on function needs to be clarified. Probe for the recent appearance of a “geriatric giant.” A full understanding of the contributing factors that are conspiring to affect an older person’s mobility can then lead to possible interventions.

## Management Strategies

The following actions may improve the future risk for falls in an older person who uses medications and has cognitive impairment:

### 1. Medications review

- Use a standardized approach, for example ARMOR [40], which is an acronym for Assess, Review, Minimize, Optimize, Reassess. A tool such as the Medication Appropriateness Index [41] is helpful to highlight those medications to consider keeping.
- Be vigilant for a recent episode of hospitalization of an older person. This is a sentinel event for prescribing problems. A medication review should be performed optimally within 1 month after hospital discharge in order to detect failures of medication reconciliation and unintentional errors and adherence issues due to communication gaps between the hospital prescriber, patient and family, and community pharmacy and community primary care provider(s).
- Aim for the lowest effective dose of an appropriate drug, including zero.
- Identify any PIMs and take the opportunity to perform “deprescribing” [35] or “medication debridement” of those drugs. A helpful Web resource which is maintained by independent researchers and contains evidence-based resources is [deprescribing.org](http://deprescribing.org).
- Evaluate the time to benefit of the drugs and weigh them against the estimated remaining years of life of the individual [23, 42].
- Discussing the goals of care and “what matters most” [43] to that patient may further modify drug treatment and pill burden.
- Review the global situation and medication list every 6 months.
- The promise of improved quality care using electronic health record systems and computer-assisted clinical decision support has not been universally achieved [44]. Be mindful that electronic systems may not be “age aware” and provide inaccurate suggestions [45].

### 2. When a potential ADE is suspected, it should be clearly documented. These documentation can help our understanding of a complex problem and develop effective strategies to improve.

### 3. Use the unspecified term: “acute functional decline” rather than assigning people labels such as “failure to thrive” or “failure to cope” which implies the patients’ accountability for their condition, which may in fact be partly iatrogenic.

### 4. Manage the person with cognitive impairment.

- Comprehensive Geriatric Assessment [46] where available, can be effective. A multidisciplinary approach to developing a feasible and sustainable plan works best.
- Increased supports from home care services, formal and informal day programs can improve socialization, well-being and medication management. Non-pharmacologic interventions for dementia in care homes may be effective but the durability is uncertain [47].

- Interventions aimed at improving prospective memory (remembering to perform an intended action at a future time) have been shown to improve medication adherence but its effects are not long lasting [48, 49].
- Use frequent human communication as a reminder system to improve medication adherence [18].

---

## Conclusions

Demographics will drive change. We need to turn health care messaging around to be positive. Appropriate medication use (optimal prescribing) should become the normal operational term. Capacity building through training more health professionals in the optimal care of older people may not be sufficient to respond to increasing need. Integrated electronic health records and properly configured computer-assisted expert decision support systems may enable access to evidence-informed best practice for many more people at risk. Individualized management plans are likely to be more successful since older people become more heterogeneous as they age. Although no targeted intervention has yet been shown to be effective [50, 51] in reliably decreasing fall risk in an older person who uses medications and has cognitive impairment, it does not mean we should give up trying. Simplifying a patient's medication profile can facilitate efforts to manage their cognitive impairment with a potential for improving the patient's quality of life as well as decreasing their fall risk and avoiding health-care costs.

---

## References

1. United Nations DoEaSA, Population Division. World population prospects: the 2017 revision, Volume II: Demographic Profiles. ST/ESA/SER.A/400, 2017.
2. Lundebjerg NE, Trucil DE, Hammond EC, Applegate WB. When it comes to older adults, language matters: Journal of the American Geriatrics Society adopts modified American Medical Association Style. *J Am Geriatr Soc.* 2017;65(7):1386–8.
3. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr.* 2017;17:230.
4. Hanlon JT, Hajjar ER. Isn't it time we stop counting the number of drugs to define polypharmacy in this new era of deprescribing and what related outcomes should be measured? *J Am Med Dir Assoc.* 2018;19(8):644–5.
5. Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. *BMJ Open.* 2015;5(12):e009235.
6. Mukker J, Singh RSP, Derendorf H. Pharmacokinetic and pharmacodynamic considerations in elderly population. In: Stegemann S, editor. *Developing drug products in an aging society from concept to prescribing.* New York: Springer; 2016. p. 139–52.
7. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. *Exp Gerontol.* 2003;38(8):843–53.
8. Bhutto AA, Morley JEAB. The clinical significance of gastrointestinal changes with aging. *Curr Opin Clin Nutr Metab Care.* 2008;11(5):651–60.

9. Wedemeyer R-S, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. *Drug Saf.* 2014;37(4):201–11.
10. Lavan AH, O'Grady J, Gallagher PF. Appropriate prescribing in the elderly: current perspectives. *World J Pharmacol.* 2015;4(2):193–209.
11. Mallet L. Pharmacology of drugs in aging. In: Huang A, Mallet L, editors. Medication-related falls in older people. Causative factors and management strategies. Cham: Springer International Publishing, Switzerland; 2016. p. 55–66.
12. Mallet L, Huang A. Coadministration of gatifloxacin and multivitamin preparation containing minerals: potential treatment failure in an elderly patient. *Ann Pharmacother.* 2005;39(1):150–2.
13. Wynne HA, Yelland C, Cope LH, Boddy A, Woodhouse KW, Bateman DN. The Association of age and frailty with the pharmacokinetics and pharmacodynamics of metoclopramide. *Age Ageing.* 1993;22(5):354–9.
14. Wynne HA, Cope LH, Herd B, Rawlins MD, James OFW, Woodhouse KW. The Association of age and frailty with paracetamol conjugation in man. *Age Ageing.* 1990;19(6):419–24.
15. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother.* 2007;5(3):263–303.
16. While C, Duane F, Beanland C, Koch S. Medication management: the perspectives of people with dementia and family carers. *Dementia.* 2012;12(6):734–50.
17. Hudani ZK, Rojas-Fernandez CH. A scoping review on medication adherence in older patients with cognitive impairment or dementia. *Res Social Adm Pharm.* 2016;12(6):815–29.
18. Campbell NL, Boustani MA, Skopelja EN, Gao S, Unverzagt FW, Murray MD. Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *Am J Geriatr Pharmacother.* 2012;10(3):165–77.
19. The American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2019;67(4):674–94.
20. Jano E, Aparasu RR. Healthcare outcomes associated with Beers' criteria: a systematic review. *Ann Pharmacother.* 2007;41(3):438–48.
21. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther.* 2008;46(2):72–83.
22. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing.* 2015;44(2):213–8.
23. Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther.* 2013;38(5):360–72.
24. Lavan AH, Gallagher P, Parsons C, O'Mahony D. STOPP/Frail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. *Age Ageing.* 2017;46(4):600–7.
25. Rochon P, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. *BMJ.* 1997;315:1096.
26. Rochon PA, Gurwitz JH. The prescribing cascade revisited. *Lancet.* 2017;389(10081):1778–80.
27. Horsley P, Huang AR. The ageing population and falls: consequences and costs. In: Huang A, Mallet L, editors. Medication-related falls in older people. Causative factors and management strategies. Springer International Publishing: Switzerland; 2016. p. 7–11.
28. Kwan E, Straus S, Holroyd-Leduc J. Risk factors for falls in the elderly. In: Huang A, Mallet L, editors. Medication-related falls in older people. Causative factors and management strategies. Cham: Springer; 2016. p. 91–101.
29. Tamblyn RM, McLeod PJ, Abrahamowicz M, Laprise R. Do too many cooks spoil the Broth? multiple physician involvement in medical management and inappropriate prescribing in the elderly. *CMAJ.* 1996;154(8):1177–84.



30. Isaacs B. *The giants of geriatrics : a study of symptoms in old age*/Bernard Isaacs. Birmingham: University of Birmingham; 1976.
31. Isaacs B. *Challenge of geriatric medicine*. Oxford: Oxford University Press; 1992. p. 254.
32. Huang A, Mallet L, editors. *Medication-Related falls in older people. Causative factors and management strategies*. Springer International Publishing: Switzerland; 2016. pp. 261.
33. Tamblyn R, Egale T, Buckeridge DL, Huang A, Hanley J, Reidel K, et al. The effectiveness of a new generation of computerized drug alerts in reducing the risk of injury from drug side effects: a cluster randomized trial. *J Am Med Inform Assoc*. 2012;19(4):635–43.
34. Dyks D. Approach to medication reviews in older adults. In: Huang A, Mallet L, editors. *Medication-related falls in older people. Causative factors and management strategies*. Springer International Publishing: Switzerland; 2016. p. 191–8.
35. Dills H, Shah K, Messinger-Rapport B, Bradford K, Syed Q. Deprescribing medications for chronic diseases management in primary care settings: a systematic review of randomized controlled trials. *J Am Med Dir Assoc*. 2018;19:923.
36. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–98.
37. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–9.
38. Borson S, Scanlan JM, Chen P, Ganguli M. The Mini-Cog as a screen for dementia: validation in a population-based sample. *J Am Geriatr Soc*. 2003;51(10):1451–4.
39. Storey JE, Rowland JTI, Conforti DA, Dickson HG. The Rowland Universal Dementia Assessment Scale (RUDAS): a multicultural cognitive assessment scale. *Int Psychogeriatr*. 2004;16(1):13–31.
40. Haque R. ARMOR: a tool to evaluate polypharmacy in elderly persons. *Ann Long-Term Care*. 2009;17(6):26–30.
41. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol*. 1992;45(10):1045–51.
42. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med*. 2006;166(6):605–9.
43. Coulter A. Measuring what matters to patients. *BMJ*. 2017;356:j816.
44. Sim I, Gorman P, Greenes RA, Haynes RB, Kaplan B, Lehmann H, et al. Clinical decision support systems for the practice of evidence-based medicine. *J Am Med Inform Assoc*. 2001;8(6):527–34.
45. Griffey RT, Lo HG, Burdick E, Keohane C, Bates DW. Guided medication dosing for elderly emergency patients using real-time, computerized decision support. *J Am Med Inform Assoc*. 2012;19(1):86–93.
46. Pilotto A, Cella A, Pilotto A, Daragjati J, Veronese N, Musacchio C, et al. Three decades of comprehensive geriatric assessment: evidence coming from different healthcare settings and specific clinical conditions. *J Am Med Dir Assoc*. 2017;18(2):192.e1–e11.
47. Cooper C, Mukadam N, Katona C, Lyketsos CG, Ames D, Rabins P, et al. Systematic review of the effectiveness of non-pharmacological interventions to improve quality of life of people with dementia. *Int Psychogeriatr*. 2012;24(6):856–70.
48. Insel KC, Einstein GO, Morrow DG, Koerner KM, Hepworth JT. Multifaceted prospective memory intervention to improve medication adherence. *J Am Geriatr Soc*. 2016;64(3):561–8.
49. Shelton JT, Lee JH, Scullin MK, Rose NS, Rendell PG, McDaniel MA. Improving prospective memory in healthy older adults and individuals with very mild Alzheimer's disease. *J Am Geriatr Soc*. 2016;64(6):1307–12.
50. Shaw FE, Bond J, Richardson DA, Dawson P, Steen IN, McKeith IG, et al. Multifactorial intervention after a fall in older people with cognitive impairment and dementia presenting to the accident and emergency department: randomised controlled trial. *BMJ*. 2003;326(7380):73.
51. Panel on Prevention of Falls in Older Persons AGS, British Geriatrics S. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc*. 2011;59(1):148–57.





# Neurobiology of Falls: Neuroimaging Assessment

# 10

Andrea L. Rosso, Neelesh K. Nadkarni,  
and Caterina Rosano

## Overview

Community-dwelling older adults without neurological diseases often report falling in the absence of a clear cause or acute health event, such as stroke. For these adults, the causes of falls are multifactorial, thus difficult to diagnose, and therefore, to treat. Age-related changes in the central nervous system (CNS) are emerging as potential neurobiological drivers of falls in older adults who are otherwise neurologically healthy. The neurobiology of falls has been studied for patient populations with Parkinson's disease and other movement disorders of neurological origin. However, studies examining these associations in community-dwelling older adults without apparent neurologic disease are sparse.

There is a strong biological rationale supporting age-related neurobiological changes as causes of falls among community-dwelling older adults. The CNS controls several biomechanical aspects of mobility, such as gait variability, speed, and balance; in turn, these are well-known causes of falls in community-dwelling older adults [1–4]. Thus, age-related changes in the CNS may compromise mobility metrics, such as increased gait variability and reduced speed and balance control, which in turn increase the risk for falls. Such CNS changes may also reduce general executive cognitive function, in particular, processing speed, and the capacity to rapidly integrate internal and external information, which are required for walking. Studies

---

A. L. Rosso · C. Rosano (✉)

University of Pittsburgh Graduate School of Public Health, Department of Epidemiology,  
Pittsburgh, PA, USA

e-mail: [ALR143@pitt.edu](mailto:ALR143@pitt.edu); [RosanoC@edc.pitt.edu](mailto:RosanoC@edc.pitt.edu)

N. K. Nadkarni

University of Pittsburgh School of Medicine, Department of Medicine (Division of Geriatric Medicine), Department of Neurology, and the Alzheimer's Disease Research Center,  
Pittsburgh, PA, USA

e-mail: [nkn3@pitt.edu](mailto:nkn3@pitt.edu)

© Springer Nature Switzerland AG 2020

M. Montero-Odasso, R. Camicioli (eds.), *Falls and Cognition in Older Persons*,  
[https://doi.org/10.1007/978-3-030-24233-6\\_10](https://doi.org/10.1007/978-3-030-24233-6_10)

165

consistently show inverse associations between the capacity to rapidly process information and fall risk [1–3]. Indeed, the capacity to adapt gait to environmental perturbations (e.g., encountering an icy patch while walking, negotiating slopes, overcoming obstacles in the path) in order to avoid a fall relies on rapid processing and integration of internal and external stimuli at the level of the CNS. Emerging evidence shows that age-related changes in CNS integrity, such as lower neurotransmission, especially affecting the cholinergic and dopaminergic systems, as well as cerebral small vessel disease, are associated with both slower processing speed, poorer gait characteristics, and falls [5]. Based on this evidence, age-related CNS changes may lead to higher fall risk via two complementary pathways: poorer biomechanics (e.g., slower and more variable gait) and reduced executive control function. These age-related impairments may further increase vulnerability to falls when exposed to environmental challenges, either in combination with changes to executive function and gait or independent of them.

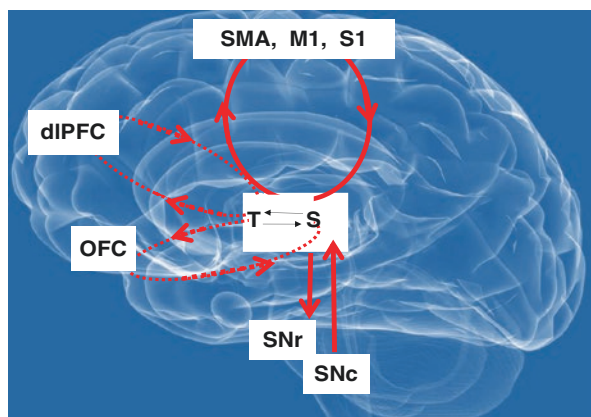
The intent of this chapter is to provide an overview of the use of neuroimaging modalities to further our understanding of the neurobiological and mechanistic underpinnings of aging that are associated with falls in older adults.

---

## Neurobiological Drivers of Falls

The spatial localization of age-related CNS characteristics is relevant to understanding the neurobiological drivers of falls. The networks of the CNS most affected by aging-related process include fronto-parietal and subcortical/basal ganglia regions and connecting tracts as well as the connecting white matter tracts [6]. The increased susceptibility of these regions derives from their location along inter-territorial borders of nonanastomosing watershed arterial systems. It is proposed that such terminal vascularization makes these regions vulnerable to disturbances of cerebral perfusion in older age, thus leading to impairments in psychomotor speed, executive control function, and gait. Thus, the fronto-parietal and subcortical regions are likely central components to the neural mechanisms of falls, due to their susceptibility to age-related changes and their roles in executive control and gait function [1].

The fronto-parietal and subcortical regions also govern motor coordination and learning [7]. The nigrostriatal dopaminergic system is of interest because it regulates sensorimotor control and execution of automatic motor tasks [8]. This system (see Fig. 10.1) extends from the brainstem to fronto-parietal areas via its dense connections in the basal ganglia. The initiation of automatic motor tasks is thought to involve a shift from anterior prefrontal networks to posterior sensorimotor cortico-striatal networks [9]. In the absence of disease, higher nigrostriatal dopamine (DA) levels have a net effect of facilitating striato-pallidum-thalamic excitatory outputs to primary sensorimotor regions, promoting ease and fluidity of movements and initiation and execution of coordinated sequences of musculoskeletal activations [10]. Similarly, the brain cholinergic system has been involved in falls mechanism in aging and PD, in particular, associated with decreased thalamic cholinergic denervation likely reflecting pedunculopontine nucleus dysfunction as described in Chap. 20.



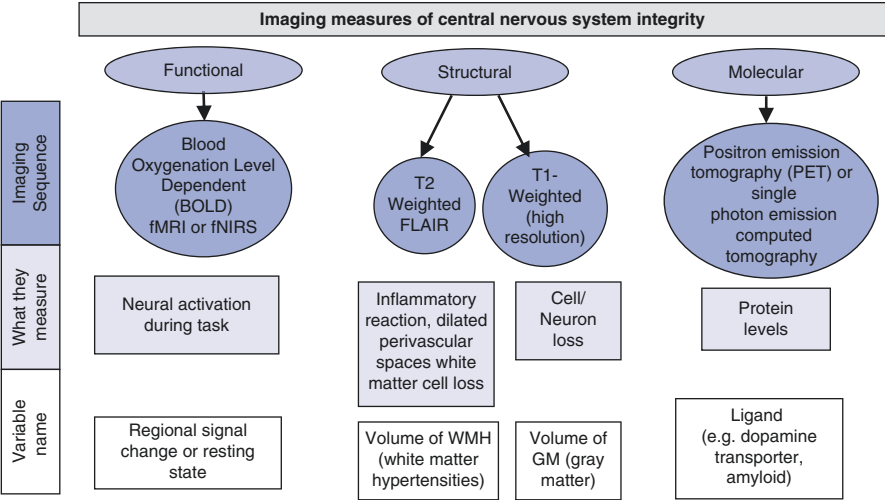
**Fig. 10.1** Simplified diagram of the nigro-striatal DA network (red solid lines). Striatum, **S**; thalamus, **T**. DA is delivered to the posterior striatum via tonically discharging fibers from the substantia nigra pars compacta (**SNc**). DA in the striatum modulates (a) excitatory inputs from sensorimotor thalamic and cortical areas (primary sensory/ motor (**S1**, **M1**), supplemental motor area (**SMA**)) and (b) inhibitory outputs to sensorimotor pallido-thalamic-cortical areas and brainstem (substantia nigra pars reticulata (**SNr**)). Dashed red lines: association network (antero-dorsal striatum, dorsolateral prefrontal cortex (**dIPFC**)); and reward network (ventral striatum, orbitofrontal cortex (**OFC**), limbic cortices). Projections to pallidum, subthalamic nucleus, and cerebellum are omitted for simplicity

In summary, age-related abnormalities in the fronto-parietal and subcortical, primarily basal ganglia, regions and connecting tracts are common and likely of vascular and neurodegenerative origin. It follows that it is important to capture the spatial distribution of age-related CNS characteristics because the localization of an abnormality within the CNS can help identify the neurobiological mechanisms leading to fall risk, leading to better and more targeted intervention strategies. In the next section, we summarize the literature linking age-related CNS characteristics, as measured via neuroimaging, with falls.

## Using Neuroimaging to Understand the Neurobiological Drivers of Falls

Neuroimaging provides the ability to assess parenchyma and ventricular integrity including integrity of tracts, regional and global cortical atrophy, burden of small-vessel disease, and ischemic changes besides others detailed below.

The clinical use of CNS neuroimaging in understanding etiology, differential diagnosis, and sequelae of falls related to overt neurological disease is reasonably well established. However, evidence for neurobiological drivers of falls for neurologically intact older adults is a very recent development in the field. The application of CNS imaging technology to understand the processes underlying age-related changes in physical function has produced important discoveries in the past two



**Fig. 10.2** Diagram summarizing the neuroimaging modalities reviewed in this chapter

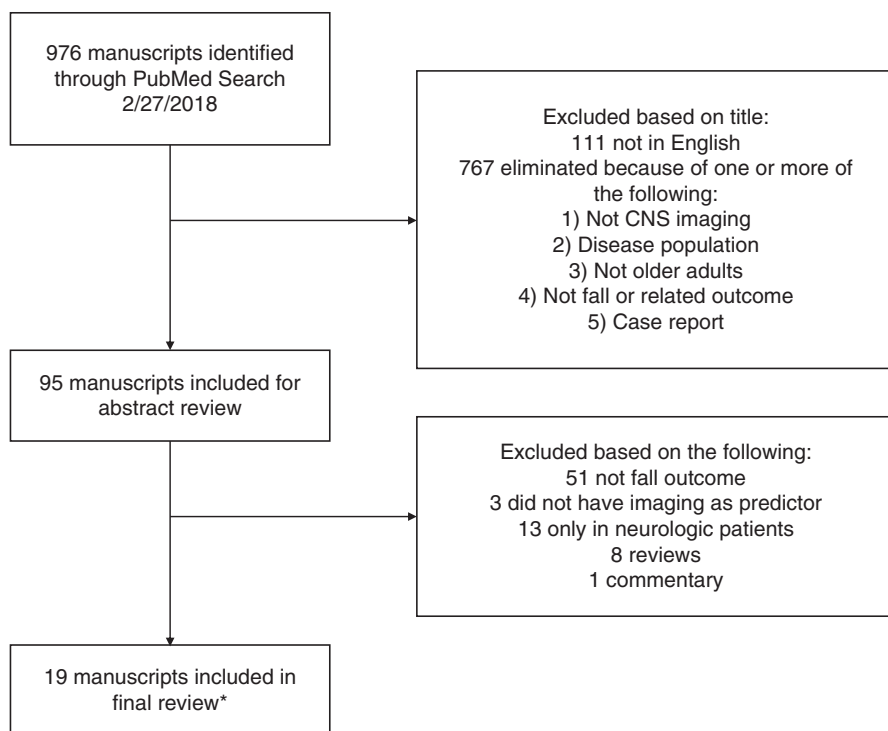
decades alone [4, 5, 11–13]. It is expected that innovations in neuroimaging techniques can advance our understanding of the neurobiological drivers of fall risk in community-dwelling older adults. Below, we provide a brief introduction to the most relevant modalities of neuroimaging used to assess age-related changes to the CNS (see Fig. 10.2) and review the existing literature (see Fig. 10.3) using these modalities to further our understanding of neurobiological drivers of fall risk.

**Neuroimaging Markers of Age-Related CNS Structure**

Magnetic resonance imaging (MRI) is the primary modality used in studies of aging CNS. MRI utilizes the magnetic properties of water molecules naturally present in the tissue to image structures and processes. MRI allows for quantification of the CNS parenchyma, including atrophy and white matter damage. Some early studies have utilized computerized tomography (CT) scans to quantify structural characteristics. However, due to its lower resolution and exposure to ionizing radiation compared to MRI, CT is now largely restricted to clinical imaging.

Gray matter atrophy is visible on MRI as enlarged ventricles, widening of the sulci, and thinning of the cortex. Such features can be rated visually using prespecified ordinal scales. Gray matter volume (GMV), a marker of atrophy, can be quantified and measured as change over time in volume of the gray matter parenchyma, segmented from the other parenchymal compartments (e.g., white matter, cerebrospinal fluid) and normalized by intracranial volume. Measures of gray matter atrophy of prespecified regions-of-interest can also be normalized to volume of the total brain.

White matter hyperintensities (WMH) are a common age-related neuroradiological finding on MRI without contrast. WMH can appear as either subcortical



**Fig. 10.3** Flow chart of literature review for neuroimaging, falls, and aging. Search terms included (neuroimaging OR MRI OR magnetic resonance imaging OR DTI OR diffusion tensor OR NIRS OR near-infrared spectroscopy OR PET OR positron emission tomography OR magnetization transfer imaging OR MTI OR single-photon emission computed tomography OR SPECT OR arterial spin labelling OR ASL OR cerebral blood flow OR CBF OR magnetoencephalography OR MEG AND (falls OR falling) AND (aging OR older OR elderly OR senior). \*17 are discussed in section “[Using Neuroimaging to Understand the Neurobiological Drivers of Falls](#)” of this chapter; 2 are presented in section “[Summary and Potential for Novel Neuroimaging Studies of Falls](#)”

punctate abnormalities, confluent WMH (“patchy areas”), and/or as periventricular caps and rims. The severity of WMH can be rated visually or quantified in terms of volumes, using more automated methods as with gray matter volume. Age-related WMH of presumed vascular origin likely represent water retention in the interstitial space following inflammatory processes and reactive astrogliosis, and correspond to areas of demyelination, axonal loss and oligodendrocyte loss [14]. WMH in older adults are generally considered a marker of small vessel disease [15].

Smaller GMV and WMH have been well studied in relation to both cognition and gait in older adults without neurologic disorders. Evidence consistently indicates associations between lower GMV and WMH with general cognitive function, lower executive function, slower gait, and more variable and less steady gait [4, 6, 11, 12, 16].

### Age-Related CNS Structural Characteristics and Falls

WMH are by far the most comprehensively studied neural correlate of falls in older adults. Nine of the articles assessed WMH [17–25] with two also including infarcts [18, 19]. WMH were assessed by visual ratings on magnetic resonance imaging (MRI) [17, 20, 21, 23] or computed tomography (CT) [22] scans, or volumes were objectively quantified from MRI scans [18, 19, 24, 25]. Results consistently indicate an increased risk of falls among those with greater burden of WMH. Visual ratings of WMH by either CT [22] or MRI [17, 20] are higher for those with a history of falling compared to those without a history of falls and are higher for individuals with unexplained disequilibrium who are at increased fall risk [21]. Associations may be strongest for those with focal compared to diffuse WMH. Longitudinal associations are also present between higher visual ratings of WMH observed on MRI with increased risk of future falls [23]. Several studies have utilized two population-based cohorts of older adults in Australia to assess volumetric measurements of WMH with longitudinal fall risk [18, 19, 24, 25]. These studies have indicated that greater baseline volume of WMH is associated with greater overall fall risk [19], greater risk for multiple falls [24], and greater risk for injurious falls [25]. Greater number of infarcts in these cohorts is also associated with greater fall risk [19]. A faster progression of WMH over 2.5 years is also associated with increased fall risk, independent of baseline WMH burden [18]. Data from these Australian cohorts have consistently demonstrated a nonlinear association between WMH and fall risk such that only those with the greatest burden of WMH have increased risk [19, 24, 25].

The evidence for associations of GMV with falls is sparse. GMV was included in only two studies and in both was visually rated from MRI [21] or CT scans [22]. No studies have reported objectively quantified GMV from MRI scans in relation to falls. There was no difference in visual ratings of atrophy by CT by fall status observed among nursing home residents with two or more unexplained falls in the past year compared to residents without falls [22]. In another study, individuals with unexplained disequilibrium experienced a greater number of falls over 5 years compared to age- and sex-matched controls and had greater frontal atrophy and greater ventricular enlargement by visual rating of MRI. However, no direct comparison of MRI findings with falls was conducted [21]. Neither of these studies assessed the role of cognitive function or gait in the relation between atrophy and falls.

In sum, most neuroimaging studies of falls have used visual estimates or volumetric measures of gray matter atrophy and WMH. A major limitation of conventional volumetric CNS imaging measures is that they cannot differentiate the cellular versus noncellular volumetric components. In fact, volumetric estimates, even when obtained for individual tracts or regions, cannot quantify the underlying pathological processes affecting neurons and connecting tracts because they do not correspond to cellular changes. White matter volume does not estimate actual intact myelin content, and smaller volume of a region does not necessarily reflect the number of neurons present. Similarly, white matter hyperintensities can be due to water retention following inflammatory processes even without myelin fragmentation [26, 27].

## **Neuroimaging Measures of Neural Activation: The Blood-Oxygen-Level-Dependent (BOLD) Response**

While spatial resolution of neuroimaging has improved with the advent of 3T and more recently 7T magnets, its use is limited in terms of determining functional or viable areas of the CNS. The modalities described in this section and section “[Neuroimaging Measures of Age-Related CNS Molecular Characteristics](#)” address these limitations in that they can assess task-related changes in cerebral blood flow, deposition of proteins, neurotransmitter loss, and altered signaling processes. Of note, drawbacks of these modalities include poorer spatial resolution and for molecular imaging, higher radiation exposure than structural MRI.

During neuronal activation, neurovascular coupling ensures that there is a local increase in blood flow due to neural oxygen utilization. This leads to an increased ratio of oxygenated ( $O_2Hb$ ) versus deoxygenated hemoglobin (HHb) [28, 29] that is spatially co-located with the neural activation. These changes are referred to as the blood-oxygen-level-dependent (BOLD) response. Functional neuroimaging methods have been developed to detect the BOLD response in order to infer about neuronal activation patterns. Two primary applications of functional neuroimaging have been developed that measure the BOLD response either during task performance or during resting state.

The functional circuit involved in a particular task can be identified by contrasting measures acquired during the task to those obtained when doing a “control” task. The most consistent pattern of CNS activation in older age seems to be a loss of asymmetry with additional areas of activation and/or greater activation within the same areas [30–39]. Whereas younger subjects show unilateral activation on a cognitive task, elderly subjects show activation of regions in both hemispheres. This is referred to as the HAROLD (hemispheric asymmetry reduction of OLD age) model [37, 40]. CNS imaging studies have shown that there is declining cognitive performance as the neuronal activation and metabolism in regions that are involved in executive control function [41–43]. Despite previous substantial work to produce a unifying conceptual model [30, 35, 37, 39, 44] it is not clear whether increased CNS activation is a response to underlying CNS structural abnormalities to maintain performance or whether it is a ‘dedifferentiation’ that follows degeneration. As Park and Reuter-Lorenz point out in their recent review on the adaptive CNS, structure and function of the CNS must be studied concurrently to understand decline in older age [45]. Others have shown that greater activation can result from the imbalance between task difficulty and neural/behavioral resources of the individual [37–39, 46–50]. In summary, the BOLD response may be increased and more generalized to other regions either because the task increases in difficulty or because localized CNS damage diminishes the availability of neural resources that are usually employed. What appears to be an increase in activation could also be due to decreased oxygen extraction in a region where there is tissue damage, atrophy, or changes in cerebral blood flow.

More recently, functional CNS imaging of the BOLD signal during resting state has been applied to understand functional networks in the CNS. Resting state imaging relies on co-activation patterns of spatially distinct regions of the CNS that may



be functionally linked. These co-activation patterns can be assessed as correlated BOLD signals between regions when a participant is not explicitly performing a task. Resting state imaging has led to the discovery of several functional networks, including the default mode network, executive control network, and sensory/motor network.

**Functional Magnetic Resonance Imaging (fMRI)** fMRI relies on the differences in magnetic properties of O<sub>2</sub>Hb and HHb. HHb has greater magnetic attraction than O<sub>2</sub>Hb and distorts the local magnetic field present in the MRI scanner. This distortion can be detected and interpreted either in the context of changes in response to a task (task-based) or correlations between regions (resting state). Based on the BOLD theory outlined above, these fluctuations in fMRI signal are interpreted as local neuronal activity. One major disadvantage of fMRI is the need to have the person being scanned lie in the confined space of the MRI machine. This limits the types of tasks that can be performed during task-based assessments. However, the spatial resolution and CNS coverage obtained from fMRI is superior to most other available methods, making it a standard for functional imaging. Nearly three decades of research with fMRI have established the relation between functional measures of the BOLD signal in specific regions of the CNS, particularly in the frontal and parietal lobes, with executive control function [51, 52]. Due to the physical constraints posed by fMRI assessment, it has been less widely used to study CNS networks related to mobility. However, studies of imagined walking while lying in the scanner have been used to explore age-related differences in CNS activation, with an emphasis on supplementary motor areas, basal ganglia, and prefrontal regions [11]. Several studies have assessed associations between resting state connectivity in the scanner with gait outside the scanner [53–56]. These studies have demonstrated associations between altered functional network connectivity and poorer mobility measures, including gait speed at normal pace and dual-task conditions, gait variability, and the Short Physical Performance Battery (SPPB). While these studies are small and largely represent preliminary findings, they have consistently demonstrated reduced within network connectivity and increased between network connectivity with poorer mobility performance [53–56].

**Functional Near-Infrared Spectroscopy (fNIRS)** fNIRS is a versatile noninvasive neuroimaging technique that measures the BOLD response. fNIRS currently represents the only functional neuroimaging modality for use while study participants are upright and walking [57, 58] and has been increasingly used to study CNS activation during physical function tasks [59]. It is also useful for settings and populations where MRI is not feasible, such as in those older generation metallic implants and shrapnel [60]. fNIRS relies on the differential absorption of near-infrared light by O<sub>2</sub>Hb and HHb. Near-infrared light is shown on the surface of the head. The light then scatters through tissue and is detected by a photo diode several centimeters from the light source. There is little absorption of near-infrared light by most tissues, with the notable exception of hemoglobin. The absorption spectrum of hemoglobin differs by its oxygenation status, allowing for discrimination between O<sub>2</sub>Hb



and HHb [29]. Due to limitations in measuring the actual path length when using continuous-wave NIRS instrumentation, absolute values of hemoglobin cannot be measured, but relative changes in concentration from a baseline condition to the task condition can be accurately recorded [29]. Continuous wave instruments are the most commonly used instruments in gait and falls research due to their low cost and ease of use. Therefore, the choice of the appropriate baseline condition for comparison is a crucial consideration in most research involving fNIRS. The major limitation of fNIRS methods is that measurements are limited to only the cortical surface of the CNS due to the reliance on light to enter the tissue and diffuse back out to the detector. Due to accessibility and ease of measurement at the prefrontal cortex, most fNIRS studies focus on this area. As a result, functional activation by fNIRS is largely used for studies of executive function where it has been used to demonstrate the increased reliance on prefrontal cortical activation in older compared to younger adults for many activities [61]. fNIRS methods have their greatest strength in their ability to be used in ecologically valid settings which has made them particularly useful for understanding cortical control of complex balance [62] and gait tasks [59]. These are most often studied in the context of dual-task performance where a motor task and a cognitive task are performed concurrently. These studies have been fairly consistent in demonstrating an age-related increase in prefrontal cortex reliance during dual-tasks though results vary depending on the specific characteristics of both the motor and the cognitive task [11, 59].

### Neuroimaging Measures of Neural Activation and Falls

Several studies have assessed associations between fall risk and task-specific functional measures [63–65] and functional near-infrared spectroscopy (fNIRS) [66, 67]. The fMRI studies all utilized an executive function (Flanker) task in the scanner [63–65] and originated from the same randomized-controlled trial of exercise in older women; these studies utilized fMRI to determine how the BOLD response during an executive function task was related to fall risk [63–65]. Collectively, these studies have demonstrated a lower BOLD response during a Flanker task in fallers compared to nonfallers with findings specific to the posterior lobe of the right cerebellum [63] and the medial frontal gyrus [64]. The role of cognitive function and gait characteristics in these relations was not explored. In the third study, the BOLD response during a Flanker task was related to the Physiological Profile Assessment (PPA), a global falls risk score. Results indicated that greater activation in the left frontal orbital cortex extending toward the insula was associated with greater declines in PPA scores during the 12-month exercise intervention [65]. In contrast, lower activation in the paracingulate gyrus extending toward the anterior cingulate gyrus was associated with greater declines in physiological falls risk over the same time period [65].

Two published studies have assessed BOLD response measured by fNIRS in relation to falls. The first study assessed prefrontal activation during a seated cognitive interference task (the Multi-Source Interference Task) with retrospective reporting of falls over the past 2 years. Performance on the cognitive task did not differ between the fallers and nonfallers [66]. However, greater O<sub>2</sub>Hb across the prefrontal

cortex was observed during the task in fallers compared to nonfallers independent of cognitive or gait performance, suggesting that fallers have less efficient prefrontal cortical processing compared to nonfallers [66]. These results are consistent with the findings in the second study where fNIRS was used to measure the BOLD signal during a walking while talking task (reciting every other letter of the alphabet while walking). Participants walked with and without a secondary cognitive task in which they recited every other letter of the alphabet [67]. Neither cognitive nor gait performance during the dual task was related to risk for falls during approximately 3 years of follow-up. However, greater prefrontal cortex activation during the walking while talking task was predictive of falls independent of cognitive or gait performance, again indicating that less efficient prefrontal cortical processing places older adults at increased risk of falls [67].

## Neuroimaging Measures of Age-Related CNS Molecular Characteristics

**Positron Emission Tomography (PET)** PET detects radiation emitted by a radio-tracer, which when injected intravenously reaches the target organ depending on the nature of the tracer that it binds to. PET has revolutionized nuclear medicine and is widely used in clinical medicine in diagnosis and management of tumors, determining cardiac risk, and in the diagnosis of neurological disorders. The applications of PET in detecting biomarkers of neurodegenerative disorders, glucose metabolism, and levels of specific neurotransmitters in the brain are shaping our understanding of the neural processes involved in gait control and falls in older adults.

Amyloid-beta (Ab) present in plaques, a key feature of Alzheimer's disease (AD) pathology, can be assessed in-situ using amyloid tracers. Pittsburgh B-positron emission tomography (PiB), a C-11 tracer, one of the first established methods of detecting Alzheimer's disease pathology in vivo on PET [68], paved the way to the development of several second-generation tracers such as florbetaben, flutemetamol, florbetapir, and, more recently, newer tracers such as F-NAV464. Ab is deposited in regions involved in mobility [69, 70]. Presence of Ab in the brain is considered a risk factor for cognitive decline and progression to AD; however, more recent literature suggests that Ab may be linked to slow gait in dementia-free older adults [71–76]. The relationship is less clear in a sample limited to cognitively normal mobility unimpaired older adults, and early evidence suggests that the relationship between Ab and slow gait may be influenced by cognition in such samples [74, 77].

Dopaminergic loss is a known contributor to impaired physical function and falls in Parkinson's disease (PD), but the neuronal losses experienced in PD are far greater than those observed in normal aging. However, there is some evidence that dopaminergic function may play a role in determining gait speed in the absence of neurologic disease [84–86]. Dopaminergic function also has known associations with cognitive function, in particular, executive function and processing speed [87]. Further, the effects of subtle dopaminergic loss experienced in aging may be

unmasked in the context of other age-related changes, specifically the concurrent loss of cholinergic neurons [5]. A number of different PET ligands exist to quantify the dopaminergic system. These ligands target different components of the system, including presynaptic markers such as the dopamine transporter (DAT) and post-synaptic components such as D<sub>1</sub> and D<sub>2</sub> receptors [88, 89]. In addition, SPECT imaging can be used to quantify many of these dopaminergic components, including DAT [88, 89]. Cholinergic loss has been also associated with future falls and fall risk in particular in individuals with PD, as described in Chap. 20.

### Age-Related Neuromolecular Characteristics and Falls

Three studies have utilized molecular imaging techniques to assess either amyloid burden [90] or dopaminergic function [91, 92] in relation to fall risk. One used positron emission tomography (PET) to visualize Ab with PiB [90]. The other two quantified dopamine transporter (DAT) presence by either PET [91] or SPECT imaging [92].

Baseline Ab burden, as measured by PiB retention, was found to be higher among older adults with a shorter time to their first fall [90]. The authors interpreted these results as evidence for preclinical Alzheimer's disease as a fall risk factor. DAT levels have been measured by either SPECT [92] or PET [91] imaging to determine dopaminergic function in relation to falls in adults without Parkinson's disease or related neurologic disorders. One study measured DAT levels by SPECT in the caudate, putamen, and striatum for patients with recurrent falls of unknown origin [92]. They found that 6 of the 21 patients had abnormal DAT levels using standard clinical cut points but failed to find an association between DAT binding and either duration or frequency of falls. However, this may be due to the very small sample size [92]. In the second study, striatal DAT levels measured by PET were approximately 15% lower among older adults with recurrent falls over a 6-month follow-up period compared to nonrecurrent fallers [91]. These findings were independent of cognitive and motor function and provide initial evidence that the dopaminergic system may be an important determinant of motor function and fall risk even in the absence of the large striatal cell loss observed in Parkinson's disease.

---

### Summary and Potential for Novel Neuroimaging Studies of Falls

Studies on the relationship between neuroimaging and falls have only begun to emerge in the last decade or so. Among the 17 articles reviewed above, all but 2 were published since 2005.

Neuroimaging studies of falls spanned a range of assessments of age-related characteristics of CNS structure, function, and molecular integrity. However, for the most part studies used single modality approaches, e.g., they measured WMH in isolation from functional and/or metabolic characteristics. Since these modalities offer complementary information of CNS integrity, they should be combined in multimodal imaging studies to further our understanding of the neural mechanisms

of falls in older age. There is also the need to conduct multinetwork studies to move beyond motor networks. With the advances in our understanding of fall risk, subtle impairments in nonmotor systems have come to the forefront as potential causes of falls; these include large-scale cognitive networks and behavioral and affective syndromes that could be linked to falls in older adults.

Another opportunity for future studies is to utilize markers that capture earlier age-related CNS changes while they may still be amenable to interventions. Most studies to date have used markers of late-stage CNS abnormalities, such as WMH. More recent neuroimaging measures capture microstructural characteristics of CNS parenchyma, CNS hemodynamics, and metabolic activity. Although they have been critical to uncover the neural mechanisms of impaired physical function (e.g., slower, variable gait) [4, 11], these more recent neuroimaging measures have not yet been examined in relation to falls. We provide here some general background information pertaining to the most recently developed neuroimaging modalities. We believe the use of these modalities can substantially help move the field forward; it is our hope that our readers will consider using these methods in future studies of the neurobiology of falls.

## **Neuroimaging Markers of Micro-structural Characteristics**

Compared to commonly used CNS volumetric measurements, more advanced MRI-based measures are being used to detect earlier changes in tissue integrity and with greater spatial precision. Identification of subtle gray and white matter abnormalities, for example, using diffusion tensor imaging (DTI), can help characterize the nature of very early age-related changes at the microstructural level [93, 94]. DTI sequences measure the diffusion of water in the CNS and differ in pathobiological sensitivity from conventional MRI. They can detect structural abnormalities of cell membranes, myelin, and neuronal connections in areas where no changes in gray matter volume or in white matter hyperintensities are apparent. DTI imaging markers of CNS subclinical disease have been studied in ageing [95, 96] and in relation to psychiatric disorders or in mild cognitive impairment to investigate the prodromal phase of Alzheimer's disease [97–99], or to monitor progression of multiple sclerosis [100–103].

### **Fractional Anisotropy**

DTI can capture fiber misalignment that can occur prior to myelin degradation and inflammation. The principle of DTI is based on differences in the apparent anisotropic diffusivity of water molecules in the CNS. Since the myelin in white matter tracts restricts the directionality of diffusion, the myelinated white matter tracts are particularly well highlighted with DTI methods. A lower DTI signal indicates tract disruption, which causes water diffusion along fibers to decrease relative to diffusion perpendicular to the fibers. The use of DTI in older adults has uncovered the presence of a very fine spatial distribution of abnormalities in the frontal lobes

[103], in the periventricular WM, in the posterior limb of the internal capsule [104, 105], and in regions crucial for processing speed [106, 107], which is impaired with age. Lower fractional anisotropy is also observed in those with slower and less steady gait patterns [108–110].

### Mean Diffusivity

DTI can also capture micro-structural abnormalities of phospholipids and cholesterol at the level of cellular membranes in areas where no changes would be apparent using conventional MRI sequences [95, 96, 111]. The principle underlying mean diffusivity is that exchange of water across the cell membrane is greater if the membrane's integrity is reduced. Mean diffusivity in otherwise normal appearing gray matter is higher in older individuals [112, 113]. Mean diffusivity in the gray matter is less well studied than fractional anisotropy in the white matter, but higher mean diffusivity is associated with poorer overall cognition [114], executive function, and processing speed [115] and with more variable gait [116].

### Neuroimaging Markers of Perfusion

Cerebral blood flow (CBF) is a proxy measure of metabolic demands of the CNS parenchyma. Clinically, CBF is commonly assessed via transcranial Doppler (TCD); one study has shown an association between TCD-related measures of cerebrovascular reactivity and falls [117]. While this method provides an aggregate measure of overall CBF; it cannot measure the spatial distribution of CBF. The arterial spin labeling MRI sequence offers regional cerebral blood flow measurements (mL/g/min) by using the arterial blood water as an endogenous contrast agent and hence avoids risks of renal injury and ionizing radiation that can occur with exogenous contrasts used for CT scans [118]. This sequence may measure changes of the perfusion that precede the abnormalities of cell membrane fragmentation or fiber misalignment. Single-photon emission computed tomography (SPECT) also allows for imaging of cerebral perfusion. SPECT of the CNS is widely used to assess regional perfusion and has been used to assess changes associated with regional perfusion in neurodegenerative conditions. However, unlike arterial spin labeling, SPECT requires a radioactive ligand for mapping cerebral blood flow. The commonly used ligands are 99mTechnitium-hexamethyl-propylenamine oxime (99mTc-HMPAO) and 99mTechnetium-L, L-ethyl cysteinate dimer 99mTc-ECD). When injected intravenously these ligands distribute within the blood and react to a compound that is bound in situ in each cell providing a proxy measure of regional cerebral blood flow (rCBF) and metabolic function of the CNS region [119]. SPECT has been used to understand the neurobiology of gait control in healthy adults. For example, SPECT analysis has demonstrated that supplementary motor areas, medial primary sensorimotor areas, striatum, cerebellar vermis, and visual cortices show increased uptake on HMPAO SPECT indicative of increased CBF [120, 121]. Hypoperfusion on SPECT, indicative of reduced neural activity, was seen in the

medial frontal areas and cerebellar regions in patients with abnormalities in gait control in Parkinson's disease [122]. Another study showed hypoperfusion in the parietal regions of the brain in patients with Alzheimer's disease was linked to impairments in the performance of instrumental activities of daily living that rely on ambulation for performing functions such as cooking, cleaning, and transportation [123]. This line of research suggests that hypoperfusion in areas of the brain that control gait could play a role understanding the cortical regions involved in gait dysfunction and falls in older adults.

## Neuroimaging Markers of Metabolism

Molecular markers of metabolic activity can provide quantitative measures of glucose metabolism, which appears to precede neurodegenerative events associated with older age. Fluoro-deoxy-D-glucose (FDG)-PET uses the principle that neurons rely on glucose metabolism for their functioning. FDG, a radioactive glucose compound, is taken up by neurons and is detected using PET to measure glucose metabolism, indicative of neuronal function and synaptic health. FDG uptake at the neuronal level is associated with levels of synaptophysin, a synaptic vesicle protein, on autopsy; therefore, FDG-PET is used as a biomarker of brain metabolism to which synaptic function is key and loss of which is indicative of neurodegeneration [78]. While FDG-PET has been used to demonstrate muscle activation while walking compared to resting [79–81], few studies focused on changes in the brain. Slower gait speed, an established marker of falls in older adults, is associated with decreased glucose metabolism on FDG-PET in the prefrontal, posterior cingulate, and parietal cortices of the brain in older functionally independent women [82]. In addition, increased FDG uptake in the temporal including hippocampus, prefrontal, and primary sensorimotor areas are seen in tasks that require higher brain functions needed to adapt gait to challenging walking environments such as on a treadmill in older adults [83]. Therefore, changes in glucose metabolism are shown to link to areas of the brain that are involved in gait control and gait adaptability that are important to gait stability in older adults.

## Other Neuroimaging Markers

An emerging and very novel MRI application pertains to the quantification of CSF dynamics. We found one small study ( $n = 23$ ) [124] suggesting a potential link between CSF dynamics and fall history. Recent work has focused on another AD relevant protein called tau, which is a key player in neurofibrillary tangle pathology in AD and can be detected on PET scans using specific tau radiotracers such as AV-1541. However, there is little research on the association between tau deposition and markers of falls in older adults, and this is an area that is likely to emerge in the near future.

## **Pathways Linking CNS and Falls: Contribution of Cognitive and Biomechanical Characteristics**

Lower executive control function, due to CNS abnormalities, can lead to slower speed of processing of external and internal information while walking, thus resulting in poorer motor control and ultimately higher fall risk. Examining the role of lower executive control function in mediating the association between neuroimaging measures and falls would provide further evidence for the mechanistic link existing between neuroimaging, executive control function, and falls. Other biomechanical characteristics, such as lower muscle strength, worse peripheral nervous function, and higher body mass index, are strongly related to falls and should be examined as potential confounders. Specifically, the association between CNS and falls could vary depending on the impairment of these musculoskeletal systems.

Although several studies have shown associations between neuroimaging markers of age-related CNS changes, executive control function, and falls, for the most part these associations have been studied separately from one another. Among the neuroimaging studies of falls reviewed above, some adjusted for cognitive [13, 17, 18, 23, 67, 91] and/or physical [17, 18, 91] function, but not all have, and none has assessed whether cognition might be a mediator of the relationship. In addition, biomechanical characteristics, such as muscle strength, body mass index, and peripheral nervous system measures, were only occasionally included in models [18, 24, 25, 91, 124]. Generally, these studies did not find large differences in results when adjusting for cognitive function, physical function, or biomechanical measures. However, we did not find modeling approaches that included cognitive or physical function performance as potential mechanistic links between neuroimaging measures of age-related CNS changes and falls. Further, in several studies, cognition was assessed either by brief dementia screeners with known ceiling effect limitations or by self-reported complaints. Inclusion of tests specific to executive function that are appropriate for use in older adults with normal cognitive function would be preferred.

---

## **Other Contributors of Falls**

Several other factors could influence the reported relations between neuroimaging measures and falls. They include:

### **Assessments of Falls**

Assessment of falls is difficult, subject to recall bias, with often poor accuracy of self-report of the event, in particular, the circumstances surrounding the fall itself. Most of the studies reviewed above relied on prospective fall assessment, but many also relied on retrospective reporting. Most prospective studies ( $n = 10$ ) used at home diaries or calendars for participants to report falls [18, 19, 23–25, 63, 64, 90,



91, 117]. The remaining studies used interviews to report falls at yearly clinic visits [21] or by telephone every 2–3 months [67]. Retrospective reporting of fall history, particularly over periods of a year or more, is known to underestimate falls and fall frequency. One paper used change in a fall risk score, the Physiologic Profile Assessment (PPA), over 12 months rather than falls as the outcome. The PPA computes a global fall risk score based on dominant hand reaction time, postural sway, contrast sensitivity, proprioception, and dominant quadriceps strength and has reported 75% accuracy for predicting falls [65]. The PPA may provide an intermediate outcome measure that could provide evidence of individuals at greatest fall risk prior to onset of a fall. This is an important group to target with intervention strategies; therefore, assessment of CNS abnormalities with risk scores could provide critical prognostic information.

## Sample Size and Source of Sample

While recent neuroimaging methodologies offer measures of CNS integrity with relatively lower noise, differences among adults without neurological diseases are not very large; hence, to capture clinically meaningful differences in CNS that are associated with falls will likely require large sample sizes. Unfortunately, none of the studies reported power calculations needed to detect meaningful effects; the median number of included subjects was 106, ranging from 21 to 822 with 9 articles including samples with more than 100 participants [17–20, 24, 25, 67, 90, 117].

The source of recruitment influences the health-related characteristics of the participants, which in turn could influence both CNS integrity and falls' occurrence. Most articles utilized clinic or other convenience samples [17, 21–23, 64, 65, 92, 124]. Clinic-based samples included those that were likely to be enriched for WMH [17], neurology patients with clinical MRIs indicating presence of WMH [23], patients complaining of disequilibrium of unknown cause [21], referrals from a movement disorders clinic [92], and patients assessed for mild cognitive impairment [124]. Other sources of convenience samples included a single nursing home [22] and a randomized clinical trial of exercise [64, 65]. Three studies did not report details of their recruitment strategy [63, 66, 91]. Eight articles utilized existing cohort data with community-based recruitment strategies [18–20, 24, 25, 67, 90, 117]. However, these eight articles represent only six independent cohort studies. Many studies included exclusion criteria based on existing neurologic or psychiatric diseases, low cognitive performance assessed by the Mini-Mental State Examination, other major diseases, and inability to walk independently. Use of convenience samples can introduce selection bias and may influence study results in ways that are not always clear. For example, use of samples enriched for WMH may limit the variability observed in this measure and the ability to detect significant associations. We recommend greater use of population-based neuroepidemiologic studies from a broader range of source populations in order to enhance the generalizability of the findings. Notably, neuroimaging studies, particularly those utilizing MRI or PET modalities, have many safety-related exclusions for



enrollment that may limit the generalizability of findings. While these exclusions cannot be eliminated, their effects can be better controlled when used in the context of population-based studies [125].

## Demographics

Overall, existing studies span a wide range of age ranges from 20 to 100 though most studies include a lower age limit of between 60 and 70 years. Fall risk is highest around this age group, so inclusion of these older age ranges is critical. However, inclusion of middle-aged and possibly younger individuals allows for a better understanding of when critical neurologic changes occur. Inclusion of younger individuals may require use of either longer follow-up to observe fall outcomes or of fall risk scores such as the PPA.

The percent of women included ranged from 36% to 100%, with seven studies including  $\leq 55\%$  women [17–19, 23, 24, 67, 124] in an age demographic where women typically outnumber men. Three articles included only women [63–65], and two did not report gender distributions [25, 92]. Comprehensiveness of reporting on other demographic and health information varied greatly between studies. Differences by demographic and health variables in the associations between neuroimaging markers and fall risk have not been well studied. Therefore, it is unclear how well the reported findings can be applied to broader populations of older adults.

## Study Design

The majority of studies ( $n = 13$ ) assessed falls prospectively [18, 19, 21, 23–25, 63, 64, 67, 90, 91, 117] though follow-up methods and times differed. Follow-up times ranged from 2 months [63] to 5 years [21], with the most common being 12 months [18, 19, 23–25, 90]. Five articles used a cross-sectional design with retrospectively reported fall history in the past 6 months [124], past year [17, 20], and past 2 years [66]. The fifth article included patients reporting recurrent falls who reported on frequency and duration of falls, but no timeframe was specified for the assessment of fall history [92]. One article reported a case-control study with cases defined as those having two or more unexplained falls in the past year compared to controls with no history of falling [22]. Notably, only one study included longitudinal neuroimaging assessment and assessed changes in WMH volume by MRI over 2.5 years [18]. Studies using retrospective reporting of falls can be problematic in that direction of the association cannot be established and reverse causation may be present. For example, it is possible that experiencing a fall leads to restricted activity, thereby influencing neuroimaging markers of brain health [126, 127]. Appropriate follow-up time in longitudinal studies is also critical as follow-up times that are too short may limit the number of events observed and therefore limit statistical power. Alternatively, use of follow-up times that are too short may lead to inclusion of events that are too far removed in time from the original neuroimaging assessment. Many changes, in

the CNS or peripheral systems, could occur that are the true drivers of fall risk. Inclusion of longitudinal measures of the CNS can help with establishment of causality. In addition, longitudinal measures of peripheral contributors to fall risk can be included in analyses in a time-varying manner to account for confounding.

---

## Conclusions

Taken together, the evidence to date indicates that age-related changes in both cerebral small vessel disease and neurotransmitters systems, e.g., DA and ACH, can increase fall risk. However, the evidence to date is more phenomenological than mechanistic. There is not yet direct evidence that lower CNS integrity directly causes fall risk nor whether biomechanical, cognitive, or other characteristics mediate this causal relationship.

Future studies of the neurobiology of falls would benefit from including more comprehensive measurements of the systems contributing to falls. Integrating tests of cognition, physical function, and peripheral nervous and muscle-skeletal systems with multiple neuroimaging measures can help clarify the neurobiology of falls. Population-based studies with thorough assessments of falls in large groups of older adults would be especially valuable to ensure a representative sample with a range of function.

Understanding the neurobiology of falls can advance the management of falls in several ways. First, it can help the development of biomarkers of fall risk; neuroimaging measures could be used as biomarkers of probability of falling. Although using neuroimaging as a screening tool at the population level would be prohibitively costly, it could be helpful to identify and monitor those who have an especially higher risk for falls, for example, those with prior history of falls or who have developed specific gait changes. Secondly, if CNS changes are strong contributors of falls, it is reasonable that they could also influence the disabling processes occurring *after* a fall. Thus, neurobiological biomarkers can help identify subgroups of fallers with different probability of recovery from a fall and help guide focused rehabilitation strategies. Lastly, recent discoveries on brain plasticity underscore that CNS changes are not irreversible and indicate several promising strategies targeting the CNS that could also influence fall risk and fall-related recovery. For example, there is emerging evidence that behavioral, pharmacological, and other intervention modalities aimed at improving processing speed could promote mobility. Such interventions could potentiate the effects of current non-CNS rehabilitative approaches to reduce risk for falls.

---

## References

1. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. *Mov Disord.* 2013;28(11):1520–33.
2. Fasano A, Plotnik M, Bove F, Berardelli A. The neurobiology of falls. *Neurol Sci.* 2012;33(6):1215–23.

3. Liu Y, Chan JS, Yan JH. Neuropsychological mechanisms of falls in older adults. *Front Aging Neurosci.* 2014;6:64.
4. Rosso AL, Studenski SA, Chen WG, et al. Aging, the central nervous system, and mobility. *J Gerontol A Biol Sci Med Sci.* 2013;68(11):1379–86.
5. Sarter M, Albin RL, Kucinski A, Lustig C. Where attention falls: increased risk of falls from the converging impact of cortical cholinergic and midbrain dopamine loss on striatal function. *Exp Neurol.* 2014;257:120–9.
6. Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev.* 2006;30(6):730–48.
7. Doyon J, Bellec P, Amel R, et al. Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behav Brain Res.* 2009;199(1):61–75.
8. Graybiel AM, Aosaki T, Flaherty AW, Kimura M. The basal ganglia and adaptive motor control. *Science.* 1994;265(5180):1826–31.
9. Wu T, Hallett M. The influence of normal human ageing on automatic movements. *J Physiol.* 2005;562(Pt 2):605–15.
10. Panigrahi B, Martin KA, Li Y, et al. Dopamine is required for the neural representation and control of movement vigor. *Cell.* 2015;162(6):1418–30.
11. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci.* 2014;69(11):1375–88.
12. Tian Q, Chastan N, Bair WN, Resnick SM, Ferrucci L, Studenski SA. The brain map of gait variability in aging, cognitive impairment and dementia-A systematic review. *Neurosci Biobehav Rev.* 2017;74(Pt A):149–62.
13. Zheng JJ, Delbaere K, Close JC, Sachdev PS, Lord SR. Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. *Stroke.* 2011;42(7):2086–90.
14. Baloh RW, Vinters HV. White matter lesions and disequilibrium in older people. II. Clinicopathologic correlation. *Arch Neurol.* 1995;52(10):975–81.
15. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12(8):822–38.
16. DeCarli C. Clinically asymptomatic vascular brain injury: a potent cause of cognitive impairment among older individuals. *J Alzheimers Dis.* 2013;33(Suppl 1):S417–26.
17. Blahak C, Baezner H, Pantoni L, et al. Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: cross sectional results from the LADIS study. *J Neurol Neurosurg Psychiatry.* 2009;80(6):608–13.
18. Callisaya ML, Beare R, Phan T, et al. Progression of white matter hyperintensities of presumed vascular origin increases the risk of falls in older people. *J Gerontol A Biol Sci Med Sci.* 2015;70(3):360–6.
19. Callisaya ML, Srikanth VK, Lord SR, et al. Sub-cortical infarcts and the risk of falls in older people: combined results of TASCOG and Sydney MAS studies. *Int J Stroke.* 2014;9(Suppl A100):55–60.
20. Corti MC, Baggio G, Sartori L, et al. White matter lesions and the risk of incident hip fracture in older persons: results from the progetto veneto anziani study. *Arch Intern Med.* 2007;167(16):1745–51.
21. Kerber KA, Enrietto JA, Jacobson KM, Baloh RW. Disequilibrium in older people: a prospective study. *Neurology.* 1998;51(2):574–80.
22. Masdeu JC, Wolfson L, Lantos G, et al. Brain white-matter changes in the elderly prone to falling. *Arch Neurol.* 1989;46(12):1292–6.
23. Shen DC, Wu SL, Shi YZ, Wang S, Zhang YM, Wang CX. The correlation between white matter hyperintensity and balance disorder and fall risk: an observational, prospective cohort study. *Chronic Dis Transl Med.* 2016;2(3):173–80.
24. Srikanth V, Beare R, Blizzard L, et al. Cerebral white matter lesions, gait, and the risk of incident falls: a prospective population-based study. *Stroke.* 2009;40(1):175–80.

25. Zheng JJ, Lord SR, Close JC, et al. Brain white matter hyperintensities, executive dysfunction, instability, and falls in older people: a prospective cohort study. *J Gerontol A Biol Sci Med Sci*. 2012;67(10):1085–91.
26. Baloh RW, Yue Q, Socotch TM, Jacobson KM. White matter lesions and disequilibrium in older people. I. Case-control comparison. *Arch Neurol*. 1995;52(10):970–4.
27. Marshall VG, Bradley WG Jr, Marshall CE, Bhooat T, Rhodes RH. Deep white matter infarction: correlation of MR imaging and histopathologic findings. *Radiology*. 1988;167(2):517–22.
28. Ferrari M, Quaresima V. A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. *NeuroImage*. 2012;63(2):921–35.
29. Scholkmann F, Kleiser S, Metz AJ, et al. A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology. *NeuroImage*. 2014;85(Pt 1):6–27.
30. Rosano C, Aizenstein H, Cochran J, et al. Functional neuroimaging indicators of successful executive control in the oldest old. *NeuroImage*. 2005;28(4):881–9.
31. Mattay VS, Fera F, Tessitore A, et al. Neurophysiological correlates of age-related changes in human motor function. *Neurology*. 2002;58(4):630–5.
32. Calautti C, Serrati C, Baron JC. Effects of age on brain activation during auditory-cued thumb-to-index opposition: a positron emission tomography study. *Stroke*. 2001;32(1):139–46.
33. Heuninckx S, Wenderoth N, Debaere F, Peeters R, Swinnen SP. Neural basis of aging: the penetration of cognition into action control. *J Neurosci*. 2005;25(29):6787–96.
34. Ward NS, Frackowiak RS. Age-related changes in the neural correlates of motor performance. *Brain*. 2003;126(Pt 4):873–88.
35. Langenecker SA, Nielson KA, Rao SM. fMRI of healthy older adults during Stroop interference. *NeuroImage*. 2004;21(1):192–200.
36. Persson J, Sylvester CY, Nelson JK, Welsh KM, Jonides J, Reuter-Lorenz PA. Selection requirements during verb generation: differential recruitment in older and younger adults. *NeuroImage*. 2004;23(4):1382–90.
37. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. *NeuroImage*. 2002;17(3):1394–402.
38. Rypma B, D'Esposito D. Age-related changes in brain-behaviour relationships: evidence from event-related functional MRI studies. *Eur J Cogn Psychol*. 2001;13(1&2):235–56.
39. Reutter-Lorenz PA, Stanczak L, Miller AC. Neural recruitment and cognitive aging: two hemispheres are better than one, especially as you age. *Psychol Sci*. 1999;10(6):494–500.
40. Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging*. 2002;17(1):85–100.
41. Elgh E, Larsson A, Eriksson S, Nyberg L. Altered prefrontal brain activity in persons at risk for Alzheimer's disease: an fMRI study. *Int Psychogeriatr*. 2003;15(2):121–33.
42. Encinas M, De Juan R, Marcos A, et al. Regional cerebral blood flow assessed with 99mTc-ECD SPET as a marker of progression of mild cognitive impairment to Alzheimer's disease. *Eur J Nucl Med Mol Imaging*. 2003;30(11):1473–80.
43. Piert M, Koeppe RA, Giordani B, Berent S, Kuhl DE. Diminished glucose transport and phosphorylation in Alzheimer's disease determined by dynamic FDG-PET. *J Nucl Med*. 1996;37(2):201–8.
44. Rosano C, Aizenstein HJ, Cochran JL, et al. Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. *Biol Psychiatry*. 2005;57(7):761–7.
45. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol*. 2009;60:173–96.
46. Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. *Curr Opin Neurobiol*. 2005;15(2):245–51.
47. Grady CL. Introduction to the special section on aging, cognition, and neuroimaging. *Psychol Aging*. 2002;17(1):3–6.

48. Madden DJ, Turkington TG, Provenzale JM, et al. Adult age differences in the functional neuroanatomy of verbal recognition memory. *Hum Brain Mapp.* 1999;7(2):115–35.
49. McIntosh AR, Sekuler AB, Penpeci C, et al. Recruitment of unique neural systems to support visual memory in normal aging. *Curr Biol.* 1999;9(21):1275–8.
50. Reuter-Lorenz PA, Marshuetz C, Jonides J, Smith EE. Neurocognitive ageing of storage and executive processes. *Eur J Cogn Psychol.* 2001;13:257–8.
51. Gratton G, Cooper P, Fabiani M, Carter CS, Karayanidis F. Dynamics of cognitive control: theoretical bases, paradigms, and a view for the future. *Psychophysiology.* 2018;55(3).
52. Munro BA, Weyandt LL, Hall LE, Oster DR, Gudmundsdottir BG, Kuhar BG. Physiological substrates of executive functioning: a systematic review of the literature. *Atten Defic Hyperact Disord.* 2018;10(1):1–20.
53. Hsu CL, Best JR, Voss MW, et al. Functional neural correlates of slower gait among older adults with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci.* 2018;74:513.
54. Hugenschmidt CE, Burdette JH, Morgan AR, Williamson JD, Kritchewsky SB, Laurienti PJ. Graph theory analysis of functional brain networks and mobility disability in older adults. *J Gerontol A Biol Sci Med Sci.* 2014;69(11):1399–406.
55. Lo OY, Halko MA, Zhou J, Harrison R, Lipsitz LA, Manor B. Gait speed and gait variability are associated with different functional brain networks. *Front Aging Neurosci.* 2017;9:390.
56. Yuan J, Blumen HM, Verghese J, Holtzer R. Functional connectivity associated with gait velocity during walking and walking-while-talking in aging: a resting-state fMRI study. *Hum Brain Mapp.* 2015;36(4):1484–93.
57. Leff DR, Orihuela-Espina F, Elwell CE, et al. Assessment of the cerebral cortex during motor task behaviours in adults: a systematic review of functional near infrared spectroscopy (fNIRS) studies. *NeuroImage.* 2011;54(4):2922–36.
58. Huppert T, Schmidt B, Beluk N, Furman J, Sparto P. Measurement of brain activation during an upright stepping reaction task using functional near-infrared spectroscopy. *Hum Brain Mapp.* 2012;34:2817.
59. Herold F, Wiegel P, Scholkmann F, Thiers A, Hamacher D, Schega L. Functional near-infrared spectroscopy in movement science: a systematic review on cortical activity in postural and walking tasks. *Neurophotonics.* 2017;4(4):041403.
60. Huppert TJ, Karim H, Lin CC, Alqahtani BA, Greenspan SL, Sparto PJ. Functional imaging of cognition in an old-old population: a case for portable functional near-infrared spectroscopy. *PLoS One.* 2017;12(10):e0184918.
61. Agbangla NF, Audiffren M, Albinet CT. Use of near-infrared spectroscopy in the investigation of brain activation during cognitive aging: a systematic review of an emerging area of research. *Ageing Res Rev.* 2017;38:52–66.
62. Rosso AL, Cenciarini M, Sparto PJ, Loughlin PJ, Furman JM, Huppert TJ. Neuroimaging of an attention demanding dual-task during dynamic postural control. *Gait Posture.* 2017;57:193–8.
63. Liu-Ambrose TY, Nagamatsu LS, Handy TC, Leghari A. Does impaired cerebellar function contribute to risk of falls in seniors? A pilot study using functional magnetic resonance imaging. *J Am Geriatr Soc.* 2008;56(11):2153–5.
64. Nagamatsu LS, Boyd LA, Hsu CL, Handy TC, Liu-Ambrose T. Overall reductions in functional brain activation are associated with falls in older adults: an fMRI study. *Front Aging Neurosci.* 2013;5:91.
65. Nagamatsu LS, Hsu CL, Handy TC, Liu-Ambrose T. Functional neural correlates of reduced physiological falls risk. *Behav Brain Funct.* 2011;7:37.
66. Halliday DWR, Hundza SR, Garcia-Barrera MA, et al. Comparing executive function, evoked hemodynamic response, and gait as predictors of variations in mobility for older adults. *J Clin Exp Neuropsychol.* 2018;40(2):151–60.
67. Verghese J, Wang C, Ayers E, Izzetoglu M, Holtzer R. Brain activation in high-functioning older adults and falls: prospective cohort study. *Neurology.* 2017;88(2):191–7.
68. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol.* 2004;55(3):306–19.

69. Rowe CC, Ellis KA, Rimajova M, et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging*. 2010;31(8):1275–83.
70. Oh H, Mormino EC, Madison C, Hayenga A, Smiljic A, Jagust WJ. beta-amyloid affects frontal and posterior brain networks in normal aging. *NeuroImage*. 2011;54(3):1887–95.
71. Tian Q, Bair WN, Resnick SM, Bilgel M, Wong DF, Studenski SA. beta-amyloid deposition is associated with gait variability in usual aging. *Gait Posture*. 2018;61:346–52.
72. Wennberg AMV, Lesnick TG, Schwarz CG, et al. Longitudinal association between brain amyloid beta and gait in the Mayo Clinic study of aging. *J Gerontol A Biol Sci Med Sci*. 2017;73:1244.
73. Wennberg AMV, Savica R, Hagen CE, et al. Cerebral amyloid deposition is associated with gait parameters in the Mayo Clinic study of aging. *J Am Geriatr Soc*. 2017;65(4):792–9.
74. Nadkarni NK, Perera S, Snitz BE, et al. Association of brain amyloid-beta with slow gait in elderly individuals without dementia: influence of cognition and Apolipoprotein E epsilon4 genotype. *JAMA Neurol*. 2017;74(1):82–90.
75. Tian Q, Resnick SM, Bilgel M, Wong DF, Ferrucci L, Studenski SA. beta-amyloid burden predicts lower extremity performance decline in cognitively unimpaired older adults. *J Gerontol A Biol Sci Med Sci*. 2017;72(5):716–23.
76. Del Campo N, Payoux P, Djilali A, et al. Relationship of regional brain beta-amyloid to gait speed. *Neurology*. 2016;86(1):36–43.
77. Nadkarni NK, Lopez OL, Perera S, et al. Cerebral amyloid deposition and dual-tasking in cognitively normal, mobility unimpaired older adults. *J Gerontol A Biol Sci Med Sci*. 2017;72(3):431–7.
78. Magistretti PJ. Neuron-glia metabolic coupling and plasticity. *J Exp Biol*. 2006;209(Pt 12):2304–11.
79. Shimada H, Kimura Y, Suzuki T, et al. The use of positron emission tomography and [18F] fluorodeoxyglucose for functional imaging of muscular activity during exercise with a stride assistance system. *IEEE Trans Neural Syst Rehabil Eng*. 2007;15(3):442–8.
80. Oi N, Iwata T, Itoh M, Yamaguchi K, Tobimatsu Y, Fujimoto T. FDG-PET imaging of lower extremity muscular activity during level walking. *J Orthop Sci*. 2003;8(1):55–61.
81. Shimada H, Kimura Y, Lord SR, et al. Comparison of regional lower limb glucose metabolism in older adults during walking. *Scand J Med Sci Sports*. 2009;19(3):389–97.
82. Sakurai R, Fujiwara Y, Yasunaga M, et al. Regional cerebral glucose metabolism and gait speed in healthy community-dwelling older women. *J Gerontol A Biol Sci Med Sci*. 2014;69(12):1519–27.
83. Shimada H, Ishii K, Ishiwata K, et al. Gait adaptability and brain activity during unaccustomed treadmill walking in healthy elderly females. *Gait Posture*. 2013;38(2):203–8.
84. Metti AL, Rosano C, Boudreau R, et al. COMT genotype and gait speed changes over ten years in older adults. *J Am Geriatr Soc*. 2017. in press.
85. Rosso AL, Bohnen NI, Launer LJ, Aizenstein HJ, Yaffe K, Rosano C. Vascular and dopaminergic contributors to mild parkinsonian signs in older adults. *Neurology*. 2018;90(3):e223–9.
86. Cham R, Studenski SA, Perera S, Bohnen NI. Striatal dopaminergic denervation and gait in healthy adults. *Exp Brain Res*. 2008;185(3):391–8.
87. Backman L, Nyberg L, Lindenberger U, Li SC, Farde L. The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neurosci Biobehav Rev*. 2006;30(6):791–807.
88. Copley VL, Fujita M, Innis RB, Nathan PJ. Molecular imaging of the dopaminergic system and its association with human cognitive function. *Biol Psychiatry*. 2006;59(10):898–907.
89. Egerton A, Mehta MA, Montgomery AJ, et al. The dopaminergic basis of human behaviors: a review of molecular imaging studies. *Neurosci Biobehav Rev*. 2009;33(7):1109–32.
90. Stark SL, Roe CM, Grant EA, et al. Preclinical Alzheimer disease and risk of falls. *Neurology*. 2013;81(5):437–43.
91. Bohnen NI, Muller ML, Kuwabara H, Cham R, Constantine GM, Studenski SA. Age-associated striatal dopaminergic denervation and falls in community-dwelling subjects. *J Rehabil Res Dev*. 2009;46(8):1045–52.



92. Djaldetti R, Treves TA, Ziv I, Melamed E, Lorberboym M. 123I-FP-CIT SPECT imaging of dopamine transporters in patients with recurrent sudden falls: are such falls a distinct entity? *J Nucl Med Technol.* 2007;35(4):232–6.
93. Venkatraman V, Aizenstein H, Newman A, Rosano C. Interrelationships of brain microstructural and macrostructural abnormalities in the oldest old. ISMRM Annual Meeting. 2009.
94. Rosano C, Newman AB, Katz R, Hirsch CH, Kuller LH. Association between lower digit symbol substitution test score and slower gait and greater risk of mortality and of developing incident disability in well-functioning older adults. *J Am Geriatr Soc.* 2008;56(9):1618–25.
95. Mezzapesa DM, Rocca MA, Pagani E, Comi G, Filippi M. Evidence of subtle gray-matter pathologic changes in healthy elderly individuals with nonspecific white-matter hyperintensities. *Arch Neurol.* 2003;60(8):1109–12.
96. Fazekas F, Ropele S, Enzinger C, et al. MTI of white matter hyperintensities. *Brain.* 2005;128(Pt 12):2926–32.
97. Kantarci K, Jack CR Jr. Neuroimaging in Alzheimer disease: an evidence-based review. *Neuroimaging Clin N Am.* 2003;13(2):197–209.
98. Schuff N, Zhu XP. Imaging of mild cognitive impairment and early dementia. *Br J Radiol.* 2007;80 Spec No 2:S109–14.
99. Lim KO, Helpert JA. Neuropsychiatric applications of DTI - a review. *NMR Biomed.* 2002;15(7–8):587–93.
100. Ropele S, Fazekas F. Magnetization transfer MR imaging in multiple sclerosis. *Neuroimaging Clin N Am.* 2009;19(1):27–36.
101. Ge Y, Law M, Grossman RI. Applications of diffusion tensor MR imaging in multiple sclerosis. *Ann N Y Acad Sci.* 2005;1064:202–19.
102. Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J Mol Neurosci.* 2008;34(1):51–61.
103. Rovaris M, Iannucci G, Cercignani M, et al. Age-related changes in conventional, magnetization transfer, and diffusion-tensor MR imaging findings: study with whole-brain tissue histogram analysis. *Radiology.* 2003;227(3):731–8.
104. Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: evidence from diffusion tensor imaging. *NeuroImage.* 2005;26(3):891–9.
105. Salat DH, Tuch DS, Greve DN, et al. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. *Neurobiol Aging.* 2005;26(8):1215–27.
106. Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *NeuroImage.* 2008;42(2):1032–44.
107. Demnitz N, Zsoldos E, Mahmood A, et al. Associations between mobility, cognition, and brain structure in healthy older adults. *Front Aging Neurosci.* 2017;9:155.
108. Verlinden VJ, de Groot M, Cremers LG, et al. Tract-specific white matter microstructure and gait in humans. *Neurobiol Aging.* 2016;43:164–73.
109. Rosario BL, Rosso AL, Aizenstein HJ, et al. Cerebral white matter and slow gait: contribution of hyperintensities and normal-appearing parenchyma. *J Gerontol A Biol Sci Med Sci.* 2016;71(7):968–73.
110. Bruijn SM, Van Impe A, Duysens J, Swinnen SP. White matter microstructural organization and gait stability in older adults. *Front Aging Neurosci.* 2014;6:104.
111. Spilt A, Geeraedts T, de Craen AJ, Westendorp RG, Blauw GJ, van Buchem MA. Age-related changes in normal-appearing brain tissue and white matter hyperintensities: more of the same or something else? *AJNR Am J Neuroradiol.* 2005;26(4):725–9.
112. Abe O, Yamasue H, Aoki S, et al. Aging in the CNS: comparison of gray/white matter volume and diffusion tensor data. *Neurobiol Aging.* 2008;29(1):102–16.
113. Mwangi B, Hasan KM, Soares JC. Prediction of individual subject's age across the human lifespan using diffusion tensor imaging: a machine learning approach. *NeuroImage.* 2013;75:58–67.

114. Rosano C, Aizenstein HJ, Newman AB, et al. Neuroimaging differences between older adults with maintained versus declining cognition over a 10-year period. *NeuroImage*. 2012;62(1):307–13.
115. Moonen JE, Foster-Dingley JC, van den Berg-Huijsmans AA, et al. Influence of small vessel disease and microstructural integrity on neurocognitive functioning in older individuals: the DANTE study Leiden. *AJNR Am J Neuroradiol*. 2017;38(1):25–30.
116. Rosso AL, Olson Hunt MJ, Yang M, et al. Higher step length variability indicates lower gray matter integrity of selected regions in older adults. *Gait Posture*. 2014;40(1):225–30.
117. Sorond FA, Galica A, Serrador JM, et al. Cerebrovascular hemodynamics, gait, and falls in an elderly population: MOBILIZE Boston study. *Neurology*. 2010;74(20):1627–33.
118. Wang J, Licht DJ, Jahng GH, et al. Pediatric perfusion imaging using pulsed arterial spin labeling. *J Magn Reson Imaging*. 2003;18(4):404–13.
119. Waldemar G. Functional brain imaging with SPECT in normal aging and dementia. Methodological, pathophysiological, and diagnostic aspects. *Cerebrovasc Brain Metab Rev*. 1995;7(2):89–130.
120. Hanakawa T, Fukuyama H, Katsumi Y, Honda M, Shibasaki H. Enhanced lateral premotor activity during paradoxical gait in Parkinson's disease. *Ann Neurol*. 1999;45(3):329–36.
121. Fukuyama H, Ouchi Y, Matsuzaki S, et al. Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci Lett*. 1997;228(3):183–6.
122. Hanakawa T, Katsumi Y, Fukuyama H, et al. Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. *Brain*. 1999;122(Pt 7):1271–82.
123. Nadkarni NK, Levy-Cooperman N, Black SE. Functional correlates of instrumental activities of daily living in mild Alzheimer's disease. *Neurobiol Aging*. 2012;33(1):53–60.
124. Onen F, Feugeas MC, De Marco G, et al. Cerebrospinal fluid MR dynamics and risk of falls in the elderly. *J Neuroradiol Journal de neuroradiologie*. 2005;32(1):3–9.
125. Ganguli M, Lee CW, Hughes T, et al. Who wants a free brain scan? Assessing and correcting for recruitment biases in a population-based sMRI pilot study. *Brain Imaging Behav*. 2015;9(2):204–12.
126. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *NeuroImage*. 2016;131:81–90.
127. Chieffi S, Messina G, Villano I, et al. Neuroprotective effects of physical activity: evidence from human and animal studies. *Front Neurol*. 2017;8:188.



---

## **Part III**

# **Special Patients and Settings**



# Falls in Parkinson's Disease and Lewy Body Dementia

11

Stephen Joza, Richard Camicioli, and Fang Ba

## Definition and Epidemiology of Lewy Body Diseases

Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are common pathologically overlapping degenerative neurological disorders associated with the presence of brainstem and cortical intra-neuronal Lewy bodies at autopsy. Parkinsonism is defined as a motor dysfunction with bradykinesia, rigidity and typically rest tremor, and otherwise unexplained posture and gait impairment (UK brain bank). Parkinsonian disorders are common, with idiopathic PD being the most common cause [1]. These same features (with distinguishing characteristics) are also found in disorders that are associated with distinct pathologies including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), cortico-basal-ganglionic degeneration (CBGD), vascular parkinsonism (VaP) and normal pressure hydrocephalus (NPH), all of which are associated with increased early falls risk relative to PD, a feature that helps in differential diagnosis [2]. Nevertheless, PD is clearly associated with an increased falls risk as disease progresses although parkinsonism alone may be the main finding at diagnosis of the other distinct causes. Hence, assessment of falls risk is critical with any patient with parkinsonism. We will focus on studies in Lewy body disorders (ranging from PD without cognitive impairment through dementia and dementia with Lewy bodies).

While motor symptoms define parkinsonism, non-motor symptoms including mild cognitive impairment, neuropsychiatric features (including anxiety and depression), autonomic features and rapid eye movement (REM) sleep behaviour disorder can precede the diagnosis of PD, DLB and MSA [3]. These features are often present from the time motor symptoms are noted [4] and can progress over time. Some

---

S. Joza · R. Camicioli · F. Ba (✉)

Division of Neurology, Department of Medicine, University of Alberta,  
Edmonton, AB, Canada

e-mail: [joza@ualberta.ca](mailto:joza@ualberta.ca); [Richard.camicioli@ualberta.ca](mailto:Richard.camicioli@ualberta.ca); [fb@ualberta.ca](mailto:fb@ualberta.ca)

© Springer Nature Switzerland AG 2020

M. Montero-Odasso, R. Camicioli (eds.), *Falls and Cognition in Older Persons*,  
[https://doi.org/10.1007/978-3-030-24233-6\\_11](https://doi.org/10.1007/978-3-030-24233-6_11)

191

of these features can help with diagnostic accuracy of the presence of a Lewy body-related disorder [5]. Mild cognitive impairment progresses over time [6] to dementia in PD [7] and can precede PD and DLB [8]. While bradykinesia and rigidity in PD respond to dopaminergic treatment, tremor and gait or posture problems do not improve as consistently in PD with less known about levodopa response in DLB [9]. However, there is often some benefit so that optimizing treatment remains important. The other non-motor symptoms do not typically respond consistently to dopaminergic therapy [10] and the response to motor symptoms becomes less complete as cognitive impairment worsens [11]. Some features such as sleepiness, postural hypotension and freezing of gait may be exacerbated by dopaminergic medications. Dementia with Lewy bodies is defined as a dementia (cognitive dysfunction affecting activities of daily living) associated with the triad of fluctuating attention, hallucinations and parkinsonism with recent inclusion of REM sleep behaviour disorder as a supportive criterion [12]. Both PD and DLB have subcortical and cortical Lewy bodies (synuclein staining is most sensitive) and neurotransmitter deficits, particularly in the dopaminergic and cholinergic systems. Measurement of dopaminergic deficits can assist with diagnosis, but do not reliably differentiate Lewy body related disorders from MSA or PSP [13]. Thus, falls are common in all Lewy body disorders, particularly when patients have cognitive impairment and are clearly associated with increased falls risk.

---

## **Accuracy of Diagnosis for Lewy Body Disease**

Conventional CT and MRI imaging are not helpful in diagnosing Lewy body diseases, but can identify symptomatic or asymptomatic comorbid pathology such as cerebrovascular infarction or microbleeds which can contribute to gait impairment. Brainstem and cortical atrophy is seen in PSP, while cerebellar atrophy can be seen in MSA. White matter high signal change is evident in VaP and ventricular dilatation is seen in NPH, though this may be a non-specific of generalized atrophy. Dopaminergic imaging and metabolic imaging (either brain or cardiac) may be useful when there is diagnostic uncertainty [14].

---

## **Epidemiology of Falls in Lewy Body Disease**

Falls in elderly overall lead to major disabilities, poor quality of life and even mortality. In PD populations, falls reduce mobility and cause mortality. Fall rates are very high in PD with a reported prevalence ranging between 35% and 90% of PD patients for a single fall (average rate of 60.5%) [15]; among which, recurrent falls account for 39% of all falls. In DLB, patients sustained six times the number of falls compared to the control group [16]. Siracuse et al. studied 780 patients  $\geq 75$  years old who were admitted after a fall, with 89% being simple falls. Short-term mortality was 6%. The median cost of hospitalization was US\$11,000 [17], not counting

the indirect cost of loss of working hours and post-admission patient care by the caregivers and that of rehabilitation.

---

## Risk Factors for Falls in PD and DLB

Given the impact that falls have upon PD and DLB patients, having a systematic way to identify those most likely to fall would be ideal to proactively mitigate risk. Consistently, the most reliable predictor of falling is a prior history of falls [18–21]. Unfortunately, though important to recognize in order to institute supportive measures, this is of limited value when trying to implement secondary prevention strategies to prevent falls from occurring in those who have yet to fall. Nevertheless, the identification of previous falls remains important.

A framework of assessment for falls risk in those with neurological disease has been proposed [22] but is not specific to those with PD and DLB, who have higher fall rates and multiple disease-specific conditions not present in those without a Lewy body disease. Indeed, the difficulty remains teasing out PD-specific factors versus those involved in general aging [23]. An important consideration in studies of whether single or multiple falls or both were considered. A European task force identified 16 generic fall risk factors amongst the general elderly population and 15 PD-specific fall risk factors that are potentially modifiable using a multidisciplinary team approach [24], although the optimal strategy for management is not clear (Table 11.1). This is because the relative contribution of each particular risk factor and its interactions with other risk factors is difficult to establish. For example, “disease severity” is one PD-specific risk factor identified by the taskforce that is objectively measured using standardized assessment scales (e.g. MDS-UPDRS or Hoehn & Yahr), but it also encompasses many other risk factors that can be proxies for severity, such as age, disease duration, and dose and class of anti-PD medications. Moreover, motoric severity may parallel other disease-associated risk factors, notably cognitive impairment (especially fluctuations in attention, visuo-spatial impairment and impaired judgement) as well as autonomic dysfunction.

Age, per se, has at best a small predictive value for falls in PD [18, 20, 25, 26], although this risk remained statistically significant in a study that corrected for disease severity [27]. Certainly, elderly populations tend to have more severe disease and comorbidities that predispose them to falling [24], although it seems an inconsistent predictor in the PD population specifically. In several studies looking at newly diagnosed PD, falls can in fact occur quite early, as highlighted in one study in which median duration of PD diagnosis was only 6 months, yet 21% of participants had fallen within a year prior to the study, and a further 16% fell within the yearlong study period [18]. In a more recent prospective analysis of newly diagnosed, drug-naïve PD patients, approximately 15% had fallen prior to enrolment, while the cumulative incidence of falls amongst previously non-fallers was 13% at 1 year [26]. Injurious falls may even precede PD diagnosis by an even longer time period, as evidenced by a nationwide case-control study, which demonstrated an

**Table 11.1** Summary of generic and disease-specific risk factors for falls in PD

Generic risk factors	PD-specific risk factors
Increased age	Fall history
Female gender	Disease severity
Sedative medications	PD medication
Anti-psychotics	Higher doses of levodopa
Anti-cholinergics	Dopamine agonists
Anti-depressants	Anti-cholinergics
Benzodiazepines	Slow mobility
Polypharmacy ( $\geq 4$ non-PD drugs)	Shuffling and small scaled gait
Autonomic dysfunction	Freezing of gait and festination
Orthostatic hypotension	Posture
Syncope	Postural instability
Cardiac arrhythmia	Transfers
Arthrosis	Cognitive impairment
Use of an assistive device	Axial rigidity
Anxiety	Dyskinesias
Weakness due to inactivity	Long-term adverse effects of DBS
Visual and ocular motor impairment	Dual tasking
Daily use of alcohol	Urinary incontinence
Environmental hazards	
Other co-morbidities	
Vertigo	
Peripheral neuropathy	
Depression	
Osteoporosis	

Adapted from van der Marck et al. [24]

increased risk of injurious fall up to 10 years prior to diagnosis and hip fracture up to 26 years preceding PD diagnosis [28]. A positive correlation between longer disease duration and fall risk has been observed in several studies with an average age in the late 60s and disease duration ranging from 4 to 11 years. Longer disease duration is also associated with recurrent falling (i.e. multiple falls recorded within a study period) [29–31]. Conversely, the association between the use of anti-PD medications and falls risk is quite variable. Several recent prospective studies identified higher levodopa equivalent dose with increased risk [21, 25, 29] and others showing no effect [19, 30, 32]. Notably, such analyses might not, by themselves, take into account treatment efficacy.

Since the MDS-UPDRS is a standardized and ubiquitous scale for describing PD severity, non-motor features and overall function, it would be helpful if its components could indicate fall predilection. Interestingly, an association between overall motor severity, as assessed by the part III subscale of the MDS-UPDRS, is variably observed, with some studies showing a correlation on univariate analysis [19, 20, 25] while others do not [18, 21, 31]. This may be explained by the fact that the UPDRS captures many elements less likely to directly affect falls risk, such as tremor or upper limb bradykinesia, relative to other items, such as postural instability, freezing of gait or difficulty rising from a chair. One approach to highlighting specific items related to falls (and overall prognostic risk) is to classify subjects as

tremor dominant based on the UPDRS versus posture and gait impaired (PIGD) [33]. As the former elements are more amenable to treatment than the latter, it is also possible that treatment can produce a lower overall UPDRS but paradoxically increase fall risk when patient mobility improves without a concomitant improvement in balance [34]. The extension of this idea is that as UPDRS increases further, a patient's mobility may decline to the point of immobility and institutionalization, and thus, the risk of falling decreases as the patient becomes more sedentary [18].

Lending credence to the idea that PD patients alter their behaviour as their disease progresses, falls that occur in the community tend to occur in the context of ambulation or during high-attention demands, or on challenging terrain in those with earlier and less severe PD as compared to falls that occur in the home [35]. In studies that examined individual elements of the UPDRS part III subscale, one found increased fall risk with impaired speech, gait and postural stability [19], while a separate study found that the strongest predictor was rapid alternating tasks of the upper limbs [19], the reason for which is speculated to be a deficiency in cognitive or sequencing tasks.

Dementia is a significant falls risk factor in both the general population and in PD [36], although with respect to mild cognitive impairment, data is less comprehensive [37]. Some studies have identified a correlation between increased falls risk and lower MMSE score [25, 26], while others have shown no influence [18, 19, 29, 30, 32]. However, some such studies have excluded patients with cognitive impairment *a priori* based upon low MMSE screening (i.e. less than 24, indicative of dementia). This is problematic since, firstly, it might exclude some mild cognitive impairment in PD, despite its prevalence [38] and, secondly, the MMSE is insensitive to attention and executive function, both of which are more prominently affected in PD-related cognitive impairment [39], and which prior study has shown to be associated with overall fall risk and freezing of gait [40–42]. Mild cognitive impairment as assessed by the Clinical Dementia Rating Scale, including informant report of cognitive change, has shown significant correlation to falls risk in one prospective cohort study [43], although further study remains limited at present.

As highlighted above, numerous individual risk factors have been variably identified as influencing probability of falling, but the relative contribution of any one in particular is difficult to assess, given the complex interplay between them. To try to discern the interactions of individual risk factors, a number of recent prospective studies have sought to devise accurate prediction models to identify those likeliest to fall [18–21, 25, 26, 29, 30, 32, 44]. Such studies typically first identify baseline characteristics that independently discriminate fallers from non-fallers, and then subsequently perform statistical modelling to describe the probability of falling using these characteristics as independent risk factors. This has the attractive proposition that only a few independent variables synergistically increase the likelihood of an imminent fall and can therefore be critical targets for fall prevention but does not take into account variables that change over time. Results of these analyses have been quite variable between studies, however. For example, in one study of 101 patients with an average disease duration of 6 years, the best predictor of falls in their multivariate model included UPDRS score, freezing of gait, symptomatic

postural orthostatic hypotension, Tinetti balance score and postural sway with a sensitivity and specificity of 78% and 84%, respectively [19]. In another study of 113 patients with recent PD diagnosis, a fall in the preceding year, freezing of gait, MMSE score less than 28/30 and abnormal axial posture predicted fallers with 78% sensitivity and 76% specificity [25]. A third study of 121 newly diagnosed PD patients determined that the most significant predictors were slow gait speed, H&Y stage and decreased stance time with 92% and 62% sensitivity and specificity [30]. Although these studies highlight a number of key risk factors, the relative degree of contribution is inconsistent. Part of the difficulty arises from the fact that many assessments are subjectively collected (questionnaires) or one-time assessments of balance, gait and disease severity, the fact that falls are generally self-reported in fall diaries and the heterogeneity of subjects between trials.

Overall, the underlying mechanisms of fall risk remains difficult to study, given the complex interplay of such factors. Falls prevention must therefore involve an analysis of each potential risk factor individualized to the patient in order to tailor intervention appropriately.

## Approaches to Falls Prevention

### Optimizing Disease Management

Optimizing treatment to improve motor function is important in PD management (Table 11.2). Dopaminergic therapy or DBS can improve gait/balance and falls, but the response is usually not as much as other motor symptoms, such as bradykinesia or rigidity [45, 46].

### Medical Management

Falls are common in PD with disease progression. This is partially due to gradual loss of postural reflexes. The effect of dopaminergic therapy on postural balance remains controversial. Postural instability (PI) does not respond well to levodopa therapy [47], and falls risk and PI persist and progressively worsen despite levodopa therapy [48]. Levodopa treatment improves overall rigidity and bradykinesia and thus allows the patient to be more mobile to rise from a chair or ambulate. The imbalance between the persistence of PI and the ability to move faster may increase the likelihood of falling.

Freezing is a major risk factor for falls and is difficult to treat. Freezing can occur in the on or off states, when medications are generally working or not working.

**Table 11.2** Therapy interventions for falls in PD and DLB

Intrinsic	Extrinsic
Optimize medical treatment for PD	Environmental assessment and modification
Cognitive strategy	Wearable sensors
Surgical treatment (DBS at novel targets)	Embedded home sensors
Exercise	Virtual reality training, combined with complex motor tasks
Physiotherapy	Non-invasive brain stimulation



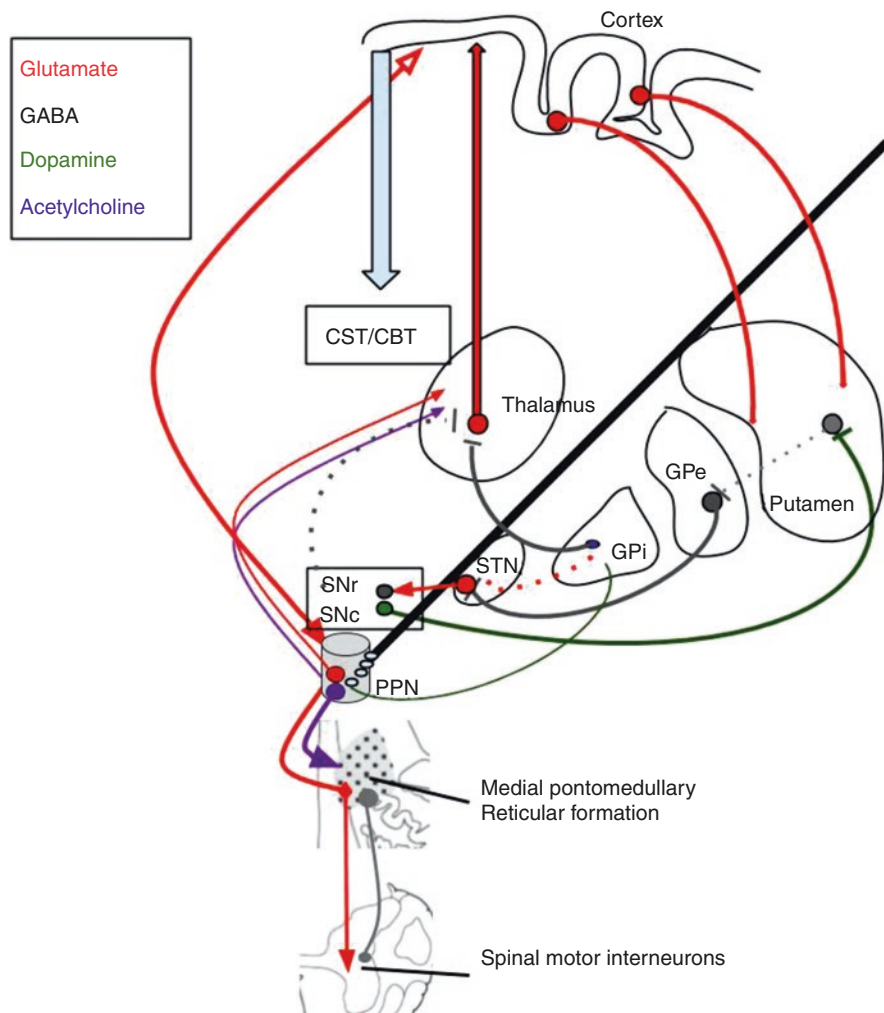
Off-freezing can improve with dopaminergic medications. However, two phase-III, prospective, double-blind, placebo-controlled trials of dopaminergic agonists on patients in early PD showed that more patients treated with agonists reported new FOG episodes during follow-up compared to those who were treated with levodopa, in spite of overall improvement in UPDRS and motor function [49, 50]. The mechanisms were not clear. On-freezing (when overall parkinsonism is improved) can be worsened with dopaminergic treatment. Selegiline was seen effective in decreasing the number of patients who develop FOG [51] and in decreasing the number of patients who will develop FOGs as a late complication of disease progression in a 2-year prospective follow-up [52]. Falls, however, were not directly addressed. Rasagiline, showed a 1.17 point improvement on the FOG-Questionnaire (FOG-Q) total score in a prospective, double blind, placebo-controlled study examining FOG severity using the FOGQ as a primary endpoint, but the clinical significance is not clear [53]. On the other hand, selective monoamine oxidase type-B inhibitors can cause orthostatic hypotension. Falls can be adverse effects from the treatment. There are conflicting results regarding amantadine in PD FOG and subsequent fall risks, but there is some evidence for fall risk reduction in progressive supranuclear palsy with amantadine [54]. The norepinephrine precursor droxidopa was shown to reduce fall risk in PD group [55]. The mechanism was attributed to improvement of postural hypotension.

Cholinergic medications might decrease falls risk in patients with PD. Specifically a small trial of donepezil suggested a reduction of falls in PD patients without FOG [56]. Another study showed improvements in gait parameters but may have been inadequately powered to examine the impact on falls [57]. Cholinergic enhancement to manage falls in PD has been summarized in Chap. 1 and reviewed in depth in Chap. 20. Conversely, anti-cholinergic burden is associated with adverse events including emergency room visits and fractures, and outcome of falls [58]. Consistent with studies in older patients, anti-depressants are associated with increased fall risk in PD [59], but it is not clear if this is related to comorbid pathology or a medication's effect.

## Surgical Management

Since the seminal study by Benabid et al. targeting the ventral intermediate nucleus (VIM) of the thalamus [60], deep brain stimulation (DBS) has emerged as a key player in the treatment of PD. Multiple randomized controlled studies have demonstrated subthalamic nucleus (STN) and globus pallidus interna (GPi)-DBS to be superior to medical treatment alone in treating a number of the cardinal symptoms and motor complications from therapy [60–62]. The benefit of DBS on axial symptoms is less clear [45]. Several reports have indicated improvement of posture, gait and balance control after STN- or GPi-DBS, when these symptoms were responsive to levodopa treatment before DBS surgery [63–68]; however, the benefit on PI and gait are not sustained [63]. Moreover, it has been noted that a significant number of patients report post-operative worsening of gait, despite concurrent improvement in motor scores and global outcomes after bilateral STN-DBS. Further, fall risk has been demonstrated to increase and levodopa-resistant FOG persists or worsens [69–75]. To complicate matters further, stimulation parameters (i.e. high frequency stimulation) can also lead to adverse axial effects in patients.

The pedunculopontine nucleus (PPN) is a key component of the mesencephalic locomotor region (MLR) [76]. Widespread projections involving the PPN include direct glutamatergic inputs from the motor cortex, and GABAergic inputs from substantia nigra, GPi, STN and deep nuclei of the cerebellum (Fig. 11.1). The PPN appears to play a key role in the initiation, acceleration, deceleration and



**Fig. 11.1** The connection motor circuit of basal ganglia with a focus of the connections to and from pedunculopontine nucleus (PPN). Deep brain stimulation at PPN target has shown some improvement in gait given its important role in locomotion. PPN contains neurons that synthesize acetylcholine,  $\gamma$ -aminobutyric acid (GABA) or L-glutamate. The PPN receives direct glutamatergic inputs from the motor cortex and GABAergic inputs from the GPi, SNr and STN and inputs from deep cerebellar nuclei. The PPN provides ascending and descending projections to the basal ganglia, SNc and thalamus. Descending projections are directed to the pontine and medullary reticular formation and the spinal cord involved that controls the locomotion.

termination of locomotion through connections to the basal ganglia and higher cortical regions [77]. Multiple open-labelled PPN-DBS studies have suggested clinical improvement in patients with PD, although results have been variable [78–81]. The first double-blinded assessment of PPN-DBS demonstrated improvement in FOG but not PI or overall UPDRS scores [82]. Moro et al. [83] showed a 75% improvement in falling, with no statistically significant changes in other motor domains with unilateral PPN-DBS. Furthermore, bilateral stimulation proved more effective than unilateral stimulation in gait control [84]. Thus, the experience and results with PPN-DBS are controversial and far from conclusive. More precise targeting strategies with improved technology (i.e. improved imaging and programming) are required. It remains to be seen whether PPN-DBS should be an adjunct target to STN- or GPi-DBS for better overall motor control.

The substantia nigra pars reticulata (SNr) is another key player in the MLR, via its significant efferent GABAergic input to the PPN [85]. The axial motor symptomatology, including gait impairment and PI, in patients with PD has shown favourable response to SNr stimulation in the literature [86–89]. However, one of the more recent double-blind, cross-over, randomized controlled trials with combined STN and SNr stimulation did show significant improvement in FOG, but not in other axial symptoms when compared to STN-DBS alone [89]. With SNr-DBS, one should be cautious about the possibility of worsening akinesia, as increased immobility and recurrent falls were reported with combined STN and SNr stimulation [89].

### **Cognitive Strategies**

We now understand better that gait is a complex motor task, and gait and cognition are interrelated. Quantifiable alterations in gait lead to falls and are also indicators for cognitive decline. Meanwhile, emerging evidence indicates that multiple domains in cognitive processes such as attention, executive function and working memory are linked to low velocity of gait and instability and fall. Fall reduction with cognitive strategies, nonpharmacological and pharmacological should be considered.

Multiple studies with single motor task, dual-task and complex motor task training have shown some benefit reducing fall risk [90–93]; however, results vary from study to study. Large-scale studies with more standardized protocols are needed.

Pharmacological interventions targeting attention and executive function have also improved gait performance in PD. Methylphenidate was shown to improve FOG presumably through improving attention [94, 95]. However, a randomized clinical trial showed negative results [96]. Cholinesterase inhibitors have been shown to provide benefit in several studies for falls in PD [58, 97], although benefit is only modest.

### **Risk Minimization**

#### **Osteoporosis**

PD patients are older, so they have a higher risk factor for metabolic bone disease in general and higher fall rate due to postural instability. These predispose PD patients

to fall-related injuries and fracture [98, 99]. Vitamin D and bisphosphonate have been used in treating bone disease in PD from a single centre [100–102]. Computed X-ray densitometry (DEXA), however, was not performed in these studies, so it is not clear if bone density was increased.

There are no specific guidelines related to management of osteoporosis and PD. A combination of bisphosphonates combined with vitamin D is recommended along with regular intake of calcium-containing food or supplements [103]. Medical treatment is mainly based on DEXA (T score < − 2.5) and FRAX scores (10-year risk for fracture > 3% hip, > 20% of any major osteoporotic fracture) [103]. Two main types of pharmacological treatments are available to treat patients with osteoporosis. Antiresorptive agents and anabolic agents have both been tried. Dietary and nutritional manipulation is important, and vitamin D, B12 and folate status need to be addressed and corrected if required. Lifestyle-related management including smoking cessation and decreasing alcohol consumption and exercise should be encouraged.

---

## Approaches to Falls Prevention in PDD and DLB

Medical treatment addressing the motor deficit in PDD and DLB is particularly challenging given the potential cognitive side effects of dopaminergic agents. Dopamine agonists and anti-cholinergic medications should be avoided in this population, given adverse effects on alertness and general cognition. With lower cognitive capacity, PDD/DLB patients are more prone to falls. Many interventions for fall prevention do not translate successfully from cognitively normal older adults to those with dementia [104], likely due to different underlying mechanisms for falls and treatment not able to address cognitive deficits adequately.

With both non-pharmacological and pharmacological treatment, one should still focus on cognitive interventions targeting attention and executive functions as well as measures improve and/or prevent further decline of balance. Concerns with metabolic bone disease and preventive measure for osteoporosis apply for PDD and DLB as well.

---

## Therapeutic Interventions

### Exercise/Physiotherapy

Exercise may be neuroprotective in PD [105, 106]. There is evidence indicating benefits of exercise programs in gait/balance, specifically strength and balance training, in reducing falls among community-dwelling older people [107–111]. Rhythmic visual or auditory clues [112–114] and mental singing during walking may also improve gait in PD [115]. Randomized controlled trials have shown fall reduction with Tai Chi [116], and exercise programs for muscle strengthening and movement strategies [117].

Physical therapy can be helpful in fall prevention [118–120], but benefit can be limited and short-lasting [121, 122]. Dosage, training intensity and duration may also affect results. A recent randomized trial of home program with strength and movement strategy training and falls education did not prevent falls [123]. Dance therapy has been observed to be beneficial and may have longer lasting effects [124–126]. In particular, tango training improved mobility and other motor domains [125].

In all therapeutic intervention studies, one should be cautious in applying the results to practice. Regular exercise, physiotherapy and dance are helpful in mobility, but the right dosage and type of exercise should be individualized. Future studies should also focus on therapy content, repetitions and effective duration, in order to optimize outcomes and cost-effectiveness for PD patients to further guide treatment.

## **Extrinsic Risk Modification**

### **Environmental Assessment and Modification**

For PD and PDD/DLB patients, fall prevention requires occupation therapy input for improvement of home environment. Such safety assessment includes, but is not limited to, foot wear, how slippery the floors are, creating safe space and familiarization with furniture layout, lighting, handrails conditions and bathroom/kitchen adaptations [127]. Patient education for behavioural adaptations is also essential to avoid [multitasking](#) and to take time with postural change to prevent postural dizziness.

### **New Devices in Fall Prevention**

Wearable sensors, such as accelerometers and gyroscopes, have been used to test mobility. Gait and balance analysis can be extracted through daily activities for a real-time fall risk assessment [128–130]. Such evaluations are potentially more sensitive than conventional tests for recording activity [131, 132]. Embedded home sensors are another approach to continuously monitor fall risk [133, 134]. There are some experiments using motion sensors to feedback and help with patients' rehabilitation. Virtual reality training, combined with complex motor tasks, has also been shown to provide some benefit in falls prevention [135].

---

## **New DBS and Non-invasive Stimulation**

In treating axial symptoms, such as FOG, multi-target DBS strategies have been trialled allowing modulation of cortico-basal ganglia loops and subsequently aiming to improve falls [136]. Targeting multiple sites can potentially synchronize different circuits and promote neuroplasticity [137]. Falls and gait impairment are likely related to multiple failing neural circuits. Evidence is supporting such notions;

combined PPN and STN stimulation appeared to have beneficial effects on gait and postural instability than either target alone [78].

Novel closed-looped adaptive DBS systems can automatically adjust the stimulation based on the real-time neural activity of a reference structure [138]. A proof-of-concept adaptive DBS study with bilateral STN-DBS, in combination with a wearable device to deliver stimulation based on local field potential beta band power of the STN [139], allowed voltage stimulation to be continuously adapted instead of on/off strategies. The study showed improvement with gait and postural stability but less stimulus-evoked side effects. Overall, better strategies are still needed for optimizing FOG and falls prevention either by choosing more ideal target(s) or by using better programming algorithm based on motor signs (i.e. using body sensors) or by monitoring neurochemical concentrations [140, 141].

Non-invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS) have been applied as treatment for various neurologic and psychiatric disorders [142]. One recent meta-analysis demonstrated that rTMS can improve motor symptoms for PD patients with a moderate effect size [143]. However, very few rTMS studies have so far focused on FOG and falls in PD [144–148]. One study with high-frequency rTMS over the lower leg primary motor cortex showed significant reduction in subjective FOG and improved gait performance [149]. However, results are not consistent with different stimulation targets, frequencies and parameters having applied. Further well-designed large-scale studies are needed.

Transcranial direct current stimulation (tDCS) is another non-invasive stimulation technique. To date, a few studies have shown some benefit of tDCS in FOG and falls. A double-blind, cross-over, randomized, sham-controlled study showed that applying 20-minutes long anodal tDCS sessions of 2 mA on M1 during rest over five consecutive days significantly reduced dopamine-resistant FOG in 10 PD patients, and the benefit persisted at one-month follow-up [150]. Simultaneous stimulation over M1 and left DLPFC with tDCS was able to modulate consecutive motor and cognitive function and further improved FOG in 20 PD individuals with FOG when compared to sham or tDCS of either target alone [151]. In practice, tDCS, compared to TMS, may be a safer, more cost-efficient tool for treatment once stronger evidence is established.

---

## Future Directions

The successful future treatment and research of falls in Parkinson's disease and related Lewy body disorders will need to consider and integrate cognitive behavioural, pharmacological, device-based and surgical treatments along with the multi-disciplinary team (exercise and occupational and physio therapy). Further research examining functional neuroanatomy and neurochemistry as well as novel imaging modalities will help with our understanding of the pathophysiology underlying gait disorders and falls and guide better treatment strategies in the future.

## References

1. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Incidence and pathology of synucleinopathies and tauopathies related to parkinsonism. *JAMA Neurol.* 2013;70(7):859–66.
2. Wenning GK, Ebersbach G, Verny M, Chaudhuri KR, Jellinger K, McKee A, et al. Progression of falls in postmortem-confirmed parkinsonian disorders. *Mov Disord.* 1999;14(6):947–50.
3. Iranzo A, Tolosa E, Gelpi E, Molinuevo JL, Valldeoriola F, Serradell M, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol.* 2013;12(5):443–53.
4. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord.* 2015;30(12):1591–601.
5. Galvin JE. Improving the clinical detection of Lewy body dementia with the Lewy body composite risk score. *Alzheimers Dement (Amst).* 2015;1(3):316–24.
6. Pedersen KF, Larsen JP, Tysnes OB, Alves G. Natural course of mild cognitive impairment in Parkinson disease: a 5-year population-based study. *Neurology.* 2017;88(8):767–74.
7. Vasconcellos LF, Pereira JS. Parkinson's disease dementia: diagnostic criteria and risk factor review. *J Clin Exp Neuropsychol.* 2015;37(9):988–93.
8. Ferman TJ, Smith GE, Kantarci K, Boeve BF, Pankratz VS, Dickson DW, et al. Nonamnesic mild cognitive impairment progresses to dementia with Lewy bodies. *Neurology.* 2013;81(23):2032–8.
9. Lucetti C, Logi C, Del Dotto P, Berti C, Ceravolo R, Baldacci F, et al. Levodopa response in dementia with lewy bodies: a 1-year follow-up study. *Parkinsonism Relat Disord.* 2010;16(8):522–6.
10. Schaeffer E, Berg D. Dopaminergic therapies for non-motor symptoms in Parkinson's disease. *CNS Drugs.* 2017;31(7):551–70.
11. Alty JE, Clissold BG, McColl CD, Reardon KA, Shiff M, Kempster PA. Longitudinal study of the levodopa motor response in Parkinson's disease: relationship between cognitive decline and motor function. *Mov Disord.* 2009;24(16):2337–43.
12. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. *Neurology.* 2017;89(1):88–100.
13. Ba F, Martin WR. Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice. *Parkinsonism Relat Disord.* 2015;21(2):87–94.
14. Surendranathan A, O'Brien JT. Clinical imaging in dementia with Lewy bodies. *Evid Based Ment Health.* 2018;21(2):61–5.
15. Allen NE, Schwarzel AK, Canning CG. Recurrent falls in Parkinson's disease: a systematic review. *Parkinsons Dis.* 2013;2013:906274.
16. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. *PLoS One.* 2009;4(5):e5521.
17. Siracuse JJ, Odell DD, Gondek SP, Odom SR, Kasper EM, Hauser CJ, et al. Health care and socioeconomic impact of falls in the elderly. *Am J Surg.* 2012;203(3):335–8.. discussion 8
18. Mactier K, Lord S, Godfrey A, Burn D, Rochester L. The relationship between real world ambulatory activity and falls in incident Parkinson's disease: influence of classification scheme. *Parkinsonism Relat Disord.* 2015;21(3):236–42.
19. Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA. Predictors of future falls in Parkinson disease. *Neurology.* 2010;75(2):116–24.
20. Pickering RM, Grimbergen YA, Rigney U, Ashburn A, Mazibrada G, Wood B, et al. A meta-analysis of six prospective studies of falling in Parkinson's disease. *Mov Disord.* 2007;22(13):1892–900.
21. Schrag A, Choudhury M, Kaski D, Gallagher DA. Why do patients with Parkinson's disease fall? A cross-sectional analysis of possible causes of falls. *NPJ Parkinsons Dis.* 2015;1:15011.
22. Thurman DJ, Stevens JA, Rao JK. Quality standards Subcommittee of the American Academy of N. practice parameter: assessing patients in a neurology practice for risk of falls



- (an evidence-based review): report of the quality standards Subcommittee of the American Academy of neurology. *Neurology*. 2008;70(6):473–9.
23. Del Din S, Galna B, Godfrey A, Bekkers EM, Nieuwhof F, et al. Analysis of free-living gait in older adults with and without Parkinson's disease and with and without a history of falls: identifying generic and disease specific characteristics. *J Gerontol A Biol Sci Med Sci*. 2017.
  24. van der Marck MA, Klok MP, Okun MS, Giladi N, Munneke M, Bloem BR, et al. Consensus-based clinical practice recommendations for the examination and management of falls in patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2014;20(4):360–9.
  25. Latt MD, Lord SR, Morris JGL, Fung VSC. Clinical and physiological assessments for elucidating falls risk in Parkinson's disease. *Mov Disord*. 2009;24(9):1280–9.
  26. Hiorth YH, Alves G, Larsen JP, Schulz J, Tysnes OB, Pedersen KF. Long-term risk of falls in an incident Parkinson's disease cohort: the Norwegian ParkWest study. *J Neurol*. 2017;264(2):364–72.
  27. Voss TS, Elm JJ, Wielinski CL, Aminoff MJ, Bandyopadhyay D, Chou KL, et al. Fall frequency and risk assessment in early Parkinson's disease. *Parkinsonism Relat Disord*. 2012;18(7):837–41.
  28. Nystrom H, Nordstrom A, Nordstrom P. Risk of injurious fall and hip fracture up to 26 y before the diagnosis of Parkinson disease: nested case-control studies in a Nationwide Cohort. *Plos Med*. 2016;13:–2.
  29. Martinolli M, Korpelainen JT, Sotaniemi KA, Myllyla VV, Korpelainen R. Recurrent falls and mortality in Parkinson's disease: a prospective two-year follow-up study. *Acta Neurol Scand*. 2011;123(3):193–200.
  30. Lord S, Galna B, Yarnall AJ, Coleman S, Burn D, Rochester L. Predicting first fall in newly diagnosed Parkinson's disease: insights from a fall-naïve cohort. *Mov Disord*. 2016;31(12):1829–36.
  31. Mak MK, Auyeung MM. The mini-BESTest can predict parkinsonian recurrent fallers: a 6-month prospective study. *J Rehabil Med*. 2013;45(6):565–71.
  32. Lord S, Galna B, Yarnall AJ, Morris R, Coleman S, Burn D, et al. Natural history of falls in an incident cohort of Parkinson's disease: early evolution, risk and protective features. *J Neurol*. 2017;264(11):2268–76.
  33. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group Neurology. 1990;40(10):1529–34.
  34. Bloem BR, Grimbergen YA, Cramer M, Willemsen M, Zwiderman AH. Prospective assessment of falls in Parkinson's disease. *J Neurol*. 2001;248(11):950–8.
  35. Lamont RM, Morris ME, Menz HB, McGinley JL, Brauer SG. Falls in people with Parkinson's disease: a prospective comparison of community and home-based falls. *Gait Posture*. 2017;55:62–7.
  36. Shaw FE. Prevention of falls in older people with dementia. *J Neural Transm (Vienna)*. 2007;114(10):1259–64.
  37. Domingos JM, Godinho C, Dean J, Coelho M, Pinto A, Bloem BR, et al. Cognitive impairment in fall-related studies in Parkinson's disease. *J Park Dis*. 2015;5(3):453–69.
  38. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS task force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. *Mov Disord*. 2011;26(10):1814–24.
  39. Yogev G, Giladi N, Peretz C, Springer S, Simon ES, Hausdorff JM. Dual tasking, gait rhythmicity, and Parkinson's disease: which aspects of gait are attention demanding? *Eur J Neurosci*. 2005;22(5):1248–56.
  40. Amboni M, Cozzolino A, Longo K, Picillo M, Barone P. Freezing of gait and executive functions in patients with Parkinson's disease. *Mov Disord*. 2008;23(3):395–400.
  41. Allcock LM, Rowan EN, Steen IN, Wesnes K, Kenny RA, Burn DJ. Impaired attention predicts falling in Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15(2):110–5.



42. Mak MK, Wong A, Pang MY. Impaired executive function can predict recurrent falls in Parkinson's disease. *Arch Phys Med Rehabil.* 2014;95(12):2390–5.
43. Camicioli R, Majumdar SR. Relationship between mild cognitive impairment and falls in older people with and without Parkinson's disease: 1-year prospective cohort study. *Gait Posture.* 2010;32(1):87–91.
44. Chou KL, Elm JJ, Wielinski CL, Simon DK, Aminoff MJ, Christine CW, et al. Factors associated with falling in early, treated Parkinson's disease: the NET-PD LS1 cohort. *J Neurol Sci.* 2017;377:137–43.
45. Ferraye MU, Deba B, Pollak P. Deep brain stimulation effect on freezing of gait. *Mov Disord.* 2008;23:S489–S94.
46. Lubik S, Fogel W, Tronnier V, Krause M, König J, Jost WH. Gait analysis in patients with advanced Parkinson disease: different or additive effects on gait induced by levodopa and chronic STN stimulation. *J Neural Transm.* 2006;113(2):163–73.
47. Klawans HL. Individual manifestations of Parkinson's disease after ten or more years of levodopa. *Mov Disord.* 1986;1(3):187–92.
48. Agid Y, Graybiel AM, Ruberg M, Hirsch E, Blin J, Dubois B, et al. The efficacy of levodopa treatment declines in the course of Parkinson's disease: do nondopaminergic lesions play a role? *Adv Neurol.* 1990;53:83–100.
49. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med.* 2000;342(20):1484–91.
50. Parkinson Study G. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA.* 2002;287(13):1653–61.
51. Giladi N, McDermott MP, Fahn S, Przedborski S, Jankovic J, Stern M, et al. Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology.* 2001;56(12):1712–21.
52. Shoulson I. DATATOP: a decade of neuroprotective inquiry. Parkinson study group. Deprenyl and tocopherol Antioxidative therapy of parkinsonism. *Ann Neurol.* 1998;44(3 Suppl 1):S160–6.
53. Rascol O, Brooks DJ, Melamed E, Oertel W, Poewe W, Stocchi F, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, lasting effect in adjunct therapy with Rasagiline given once daily, study): a randomised, double-blind, parallel-group trial. *Lancet.* 2005;365(9463):947–54.
54. Kondo T. Drug intervention for freezing of gait resistant to dopaminergic therapy: a pilot study. *Parkinsonism Relat D.* 2006;12(suppl. 2):S63–S6.
55. Hauser RA, Heritier S, Rowse GJ, Hewitt LA, Isaacson SH. Droxidopa and reduced falls in a trial of Parkinson disease patients with neurogenic orthostatic hypotension. *Clin Neuropharmacol.* 2016;39(5):220–6.
56. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. *Neurology.* 2010;75(14):1263–9.
57. Crispo JA, Willis AW, Thibault DP, Fortin Y, Hays HD, McNair DS, et al. Associations between anticholinergic burden and adverse health outcomes in Parkinson disease. *PLoS One.* 2016;11(3):e0150621.
58. Henderson EJ, Lord SR, Brodie MA, Gaunt DM, Lawrence AD, Close JC, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016;15(3):249–58.
59. Martinez-Ramirez D, Giugni JC, Almeida L, Walz R, Ahmed B, Chai FA, et al. Association between antidepressants and falls in Parkinson's disease. *J Neurol.* 2016;263(1):76–82.
60. Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol.* 1987;50(1–6):344–6.
61. Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain.* 2010;133(9):2664–76.

62. Rizzone MG, Fasano A, Daniele A, Zibetti M, Merola A, Rizzi L, et al. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: from the advanced phase towards the late stage of the disease? *Parkinsonism Relat Disord.* 2014;20(4):376–81.
63. Castrìto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol.* 2011;68(12):1550–6.
64. Cossu G, Pau M. Subthalamic nucleus stimulation and gait in Parkinson's disease: a not always fruitful relationship. *Gait Posture.* 2017;52:205–10.
65. Guzzi G, Della Torre A, Chirchiglia D, Volpentesta G, Lavano A. Critical reappraisal of DBS targeting for movement disorders. *J Neurosurg Sci.* 2016;60(2):181–8.
66. Collomb-Clerc A, Welter ML. Effects of deep brain stimulation on balance and gait in patients with Parkinson's disease: a systematic neurophysiological review. *Neurophysiologie clinique = Clin Neurophysiol.* 2015;45(4–5):371–88.
67. Okun MS, Gallo BV, Mandybur G, Jagid J, Foote KD, Revilla FJ, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol.* 2012;11(2):140–9.
68. Rodríguez-Oroz MC, Obeso JA, Lang AE, Houeto JL, Pollak P, Rehncrona S, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain.* 2005;128(Pt 10):2240–9.
69. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med.* 2010;362(22):2077–91.
70. van Nuenen BF, Esselink RA, Munneke M, Speelman JD, van Laar T, Bloem BR. Postoperative gait deterioration after bilateral subthalamic nucleus stimulation in Parkinson's disease. *Mov Disord.* 2008;23(16):2404–6.
71. Ferraye MU, Debu B, Fraix V, Xie-Brustolin J, Chabardes S, Krack P, et al. Effects of subthalamic nucleus stimulation and levodopa on freezing of gait in Parkinson disease. *Neurology.* 2008;70(16 Pt 2):1431–7.
72. McNeely ME, Earhart GM. Medication and subthalamic nucleus deep brain stimulation similarly improve balance and complex gait in Parkinson disease. *Parkinsonism Relat Disord.* 2013;19(1):86–91.
73. Crenna P, Carpinella I, Rabuffetti M, Rizzone M, Lopiano L, Lanotte M, et al. Impact of subthalamic nucleus stimulation on the initiation of gait in Parkinson's disease. *Exp Brain Res.* 2006;172(4):519–32.
74. Stolze H, Klebe S, Poepping M, Lorenz D, Herzog J, Hamel W, et al. Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait. *Neurology.* 2001;57(1):144–6.
75. Xu F, Ma W, Huang Y, Qiu Z, Sun L. Deep brain stimulation of pallidal versus subthalamic for patients with Parkinson's disease: a meta-analysis of controlled clinical trials. *Neuropsychiatr Dis Treat.* 2016;12:1435–44.
76. Tattersall TL, Stratton PG, Coyne TJ, Cook R, Silberstein P, Silburn PA, et al. Imagined gait modulates neuronal network dynamics in the human pedunculopontine nucleus. *Nat Neurosci.* 2014;17(3):449–54.
77. Lee MS, Rinne JO, Marsden CD. The pedunculopontine nucleus: its role in the genesis of movement disorders. *Yonsei Med J.* 2000;41(2):167–84.
78. Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, et al. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain.* 2007;130(Pt 6):1596–607.
79. Strafella AP, Lozano AM, Ballanger B, Poon YY, Lang AE, Moro E. rCBF changes associated with PPN stimulation in a patient with Parkinson's disease: a PET study. *Mov Disord.* 2008;23(7):1051–4.
80. Thevathasan W, Silburn PA, Brooker H, Coyne TJ, Khan S, Gill SS, et al. The impact of low-frequency stimulation of the pedunculopontine nucleus region on reaction time in parkinsonism. *J Neurol Neurosurg Psychiatry.* 2010;81(10):1099–104.
81. Khan S, Mooney L, Plaha P, Javed S, White P, Whone AL, et al. Outcomes from stimulation of the caudal zona incerta and pedunculopontine nucleus in patients with Parkinson's disease. *Br J Neurosurg.* 2011;25(2):273–80.

82. Ferraye MU, Debu B, Fraix V, Goetz L, Ardouin C, Yelnik J, et al. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. *Brain*. 2010;133(Pt 1):205–14.
83. Moro E, Hamani C, Poon YY, Al-Khairallah T, Dostrovsky JO, Hutchison WD, et al. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. *Brain*. 2010;133(Pt 1):215–24.
84. Thevathasan W, Pogosyan A, Hyam JA, Jenkinson N, Foltynie T, Limousin P, et al. Alpha oscillations in the pedunculopontine nucleus correlate with gait performance in parkinsonism. *Brain*. 2012;135(Pt 1):148–60.
85. Takakusaki K, Chiba R, Nozu T, Okumura T. Brainstem control of locomotion and muscle tone with special reference to the role of the mesopontine tegmentum and medullary reticulospinal systems. *J Neural Transm (Vienna)*. 2016;123(7):695–729.
86. Brosius SN, Gonzalez CL, Shuresh J, Walker HC. Reversible improvement in severe freezing of gait from Parkinson's disease with unilateral interleaved subthalamic brain stimulation. *Parkinsonism Relat Disord*. 2015;21(12):1469–70.
87. Chastan N, Westby GW, Yelnik J, Bardinet E, Do MC, Agid Y, et al. Effects of nigral stimulation on locomotion and postural stability in patients with Parkinson's disease. *Brain*. 2009;132(Pt 1):172–84.
88. Weiss D, Klotz R, Govindan RB, Scholten M, Naros G, Ramos-Murguialday A, et al. Subthalamic stimulation modulates cortical motor network activity and synchronization in Parkinson's disease. *Brain J Neurol*. 2015;138(Pt 3):679–93.
89. Weiss D, Walach M, Meisner C, Fritz M, Scholten M, Breit S, et al. Nigral stimulation for resistant axial motor impairment in Parkinson's disease? A randomized controlled trial. *Brain*. 2013;136(Pt 7):2098–108.
90. Verghese J, Mahoney J, Ambrose AF, Wang C, Holtzer R. Effect of cognitive remediation on gait in sedentary seniors. *J Gerontol A Biol Sci Med Sci*. 2010;65(12):1338–43.
91. Silsupadol P, Shumway-Cook A, Lugade V, van Donkelaar P, Chou LS, Mayr U, et al. Effects of single-task versus dual-task training on balance performance in older adults: a double-blind, randomized controlled trial. *Arch Phys Med Rehabil*. 2009;90(3):381–7.
92. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *J Gerontol A Biol Sci Med Sci*. 2011;66(2):234–40.
93. You JH, Shetty A, Jones T, Shields K, Belay Y, Brown D. Effects of dual-task cognitive-gait intervention on memory and gait dynamics in older adults with a history of falls: a preliminary investigation. *NeuroRehabilitation*. 2009;24(2):193–8.
94. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin Neuropharmacol*. 2006;29(1):15–7.
95. Pollak L, Dobronevsky Y, Prohorov T, Bahunker S, Rabey JM. Low dose methylphenidate improves freezing in advanced Parkinson's disease during off-state. *J Neural Transm Suppl*. 2007;72:145–8.
96. Espay AJ, Dwivedi AK, Payne M, Gaines L, Vaughan JE, Maddux BN, et al. Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. *Neurology*. 2011;76(14):1256–62.
97. Mancini M, Fling BW, Gendreau A, Lapidus J, Horak FB, Chung K, et al. Effect of augmenting cholinergic function on gait and balance. *BMC Neurol*. 2015;15:264.
98. Gregson CL, Dennison EM, Compston JE, Adami S, Adachi JD, Anderson FA Jr, et al. Disease-specific perception of fracture risk and incident fracture rates: GLOW cohort study. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2014;25(1):85–95.
99. Johnell O, Sernbo I. Health and social status in patients with hip fractures and controls. *Age Ageing*. 1986;15(5):285–91.

100. Sato Y, Iwamoto J, Honda Y. Vitamin d deficiency-induced vertebral fractures may cause stooped posture in Parkinson disease. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists*. 2011;90(4):281–6.
101. Sato Y, Iwamoto J, Honda Y. Once-weekly risedronate for prevention of hip fracture in women with Parkinson's disease: a randomised controlled trial. *J Neurol Neurosurg Psychiatry*. 2011;82(12):1390–3.
102. Sato Y, Iwamoto J, Kanoko T, Satoh K. Alendronate and vitamin D2 for prevention of hip fracture in Parkinson's disease: a randomized controlled trial. *Mov Disord*. 2006;21(7):924–9.
103. Metta V, Sanchez TC, Padmakumar C. Osteoporosis: a hidden nonmotor face of Parkinson's disease. *Int Rev Neurobiol*. 2017;134:877–90.
104. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60(11):2127–36.
105. Campos C, Rocha NB, Lattari E, Paes F, Nardi AE, Machado S. Exercise-induced neuro-protective effects on neurodegenerative diseases: the key role of trophic factors. *Expert Rev Neurother*. 2016;16(6):723–34.
106. da Silva PG, Domingues DD, de Carvalho LA, Allodi S, Correa CL. Neurotrophic factors in Parkinson's disease are regulated by exercise: evidence-based practice. *J Neurol Sci*. 2016;363:5–15.
107. Goodwin VA, Abbott RA, Whear R, Bethel A, Ukoumunne OC, Thompson-Coon J, et al. Multiple component interventions for preventing falls and fall-related injuries among older people: systematic review and meta-analysis. *BMC Geriatr*. 2014;14:15.
108. Tricco AC, Cogo E, Holroyd-Leduc J, Sibley KM, Feldman F, Kerr G, et al. Efficacy of falls prevention interventions: protocol for a systematic review and network meta-analysis. *Syst Rev*. 2013;2:38.
109. Chang JT, Morton SC, Rubenstein LZ, Mojica WA, Maglione M, Suttrop MJ, et al. Interventions for the prevention of falls in older adults: systematic review and meta-analysis of randomised clinical trials. *BMJ*. 2004;328(7441):680.
110. Sherrington C, Michaleff ZA, Fairhall N, Paul SS, Tiedemann A, Whitney J, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. *Br J Sports Med*. 2017;51(24):1750–8.
111. Rimland JM, Abbraha I, Dell'Aquila G, Cruz-Jentoft A, Soiza R, Gudmusson A, et al. Effectiveness of non-pharmacological interventions to prevent falls in older people: a systematic overview. The SENATOR project ONTOP series. *PLoS ONE*. 2016;11(8):e0161579.
112. Suteerawattananon M, Morris GS, Etnyre BR, Jankovic J, Protas EJ. Effects of visual and auditory cues on gait in individuals with Parkinson's disease. *J Neurol Sci*. 2004;219(1–2):63–9.
113. Ledger S, Galvin R, Lynch D, Stokes EK. A randomised controlled trial evaluating the effect of an individual auditory cueing device on freezing and gait speed in people with Parkinson's disease. *BMC Neurol*. 2008;8:46.
114. Arias P, Cudeiro J. Effect of rhythmic auditory stimulation on gait in parkinsonian patients with and without freezing of gait. *PLoS One*. 2010;5(3):e9675.
115. Satoh M, Kuzuhara S. Training in mental singing while walking improves gait disturbance in Parkinson's disease patients. *Eur Neurol*. 2008;60(5):237–43.
116. Li F, Harmer P, Fitzgerald K, Eckstrom E, Stock R, Galver J, et al. Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med*. 2012;366(6):511–9.
117. Morris ME, Menz HB, McGinley JL, Watts JJ, Huxham FE, Murphy AT, et al. A randomized controlled trial to reduce falls in people with Parkinson's disease. *Neurorehabil Neural Repair*. 2015;29(8):777–85.
118. Sparrow D, DeAngelis TR, Hendron K, Thomas CA, Saint-Hilaire M, Ellis T. Highly challenging balance program reduces fall rate in Parkinson disease. *J Neurol Physical Therapy: JNPT*. 2016;40(1):24–30.
119. Wong-Yu IS, Mak MK. Task- and context-specific balance training program enhances dynamic balance and functional performance in parkinsonian nonfallers: a randomized controlled trial with six-month follow-up. *Arch Phys Med Rehabil*. 2015;96(12):2103–11.

120. Shen X, Mak MK. Technology-assisted balance and gait training reduces falls in patients with Parkinson's disease: a randomized controlled trial with 12-month follow-up. *Neurorehabil Neural Repair*. 2015;29(2):103–11.
121. Morris ME, Martin C, McGinley JL, Huxham FE, Menz HB, Taylor NF, et al. Protocol for a home-based integrated physical therapy program to reduce falls and improve mobility in people with Parkinson's disease. *BMC Neurol*. 2012;12:54.
122. Frazzitta G, Maestri R, Uccellini D, Bertotti G, Abelli P. Rehabilitation treatment of gait in patients with Parkinson's disease with freezing: a comparison between two physical therapy protocols using visual and auditory cues with or without treadmill training. *Mov Disord*. 2009;24(8):1139–43.
123. Morris ME, Taylor NF, Watts JJ, Evans A, Horne M, Kempster P, et al. A home program of strength training, movement strategy training and education did not prevent falls in people with Parkinson's disease: a randomised trial. *J Physiother*. 2017;63(2):94–100.
124. McKay JL, Ting LH, Hackney ME. Balance, body motion, and muscle activity after high-volume short-term dance-based rehabilitation in persons with Parkinson disease: a pilot study. *Journal of neurologic physical therapy: JNPT*. 2016;40(4):257–68.
125. McNeely ME, Mai MM, Duncan RP, Earhart GM. Differential effects of tango versus dance for PD in Parkinson disease. *Front Aging Neurosci*. 2015;7:239.
126. Duncan RP, Earhart GM. Are the effects of community-based dance on Parkinson disease severity, balance, and functional mobility reduced with time? A 2-year prospective pilot study. *J Altern Complement Med*. 2014;20(10):757–63.
127. Binks S, Dobson R. Risk factors, epidemiology and treatment strategies for metabolic bone disease in patients with neurological disease. *Curr Osteoporos Rep*. 2016;14(5):199–210.
128. Mirelman A, Giladi N, Hausdorff JM. Body-fixed sensors for Parkinson disease. *JAMA*. 2015;314(9):873–4.
129. Morris R, Hickey A, Del Din S, Godfrey A, Lord S, Rochester L. A model of free-living gait: a factor analysis in Parkinson's disease. *Gait Posture*. 2017;52:68–71.
130. Weiss A, Herman T, Giladi N, Hausdorff JM. Objective assessment of fall risk in Parkinson's disease using a body-fixed sensor worn for 3 days. *PLoS One*. 2014;9(5):e96675.
131. Fasano A, Canning CG, Hausdorff JM, Lord S, Rochester L. Falls in Parkinson's disease: a complex and evolving picture. *Mov Disord*. 2017;32(11):1524–36.
132. Buchman AS, Leurgans SE, Weiss A, Vanderhorst V, Mirelman A, Dawe R, et al. Associations between quantitative mobility measures derived from components of conventional mobility testing and parkinsonian gait in older adults. *PLoS One*. 2014;9(1):e86262.
133. Austin D, Hayes TL, Kaye J, Mattek N, Pavel M. Unobtrusive monitoring of the longitudinal evolution of in-home gait velocity data with applications to elder care. Conference proceedings: Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference. 2011;2011:6495–8.
134. Kaye J, Mattek N, Dodge H, Buracchio T, Austin D, Hagler S, et al. One walk a year to 1000 within a year: continuous in-home unobtrusive gait assessment of older adults. *Gait Posture*. 2012;35(2):197–202.
135. Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet*. 2016;388(10050):1170–82.
136. Castrioto A, Moro E. New targets for deep brain stimulation treatment of Parkinson's disease. *Expert Rev Neurother*. 2013;13(12):1319–28.
137. Udupa K, Chen R. The mechanisms of action of deep brain stimulation and ideas for the future development. *Prog Neurobiol*. 2015;133:27–49.
138. Little S, Beudel M, Zrinzo L, Foltynie T, Limousin P, Hariz M, et al. Bilateral adaptive deep brain stimulation is effective in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2016;87(7):717–21.
139. Rosa M, Arlotti M, Ardolino G, Cogiamanian F, Marceglia S, Di Fonzo A, et al. Adaptive deep brain stimulation in a freely moving parkinsonian patient. *Mov Disord*. 2015;30(7):1003–5.

140. Kishida KT, Saez I, Lohrenz T, Witcher MR, Laxton AW, Tatter SB, et al. Subsecond dopamine fluctuations in human striatum encode superposed error signals about actual and counterfactual reward. *Proc Natl Acad Sci U S A*. 2016;113(1):200–5.
141. Van Gompel JJ, Chang SY, Goerss SJ, Kim IY, Kimble C, Bennet KE, et al. Development of intraoperative electrochemical detection: wireless instantaneous neurochemical concentration sensor for deep brain stimulation feedback. *Neurosurg Focus*. 2010;29(2):E6.
142. Wassermann EM, Lisanby SH. Therapeutic application of repetitive transcranial magnetic stimulation: a review. *Clin Neurophysiol*. 2001;112(8):1367–77.
143. Chou YH, Hickey PT, Sundman M, Song AW, Chen NK. Effects of repetitive transcranial magnetic stimulation on motor symptoms in Parkinson disease: a systematic review and meta-analysis. *JAMA Neurol*. 2015;72(4):432–40.
144. Kim MS, Hyuk Chang W, Cho JW, Youn J, Kim YK, Woong Kim S, et al. Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. *Restor Neurol Neurosci*. 2015;33(4):521–30.
145. Dagan M, Herman T, Mirelman A, Giladi N, Hausdorff JM. The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study. *Exp Brain Res*. 2017;235:2463.
146. Tard C, Devanne H, Defebvre L, Delval A. Single session intermittent theta-burst stimulation on the left premotor cortex does not alleviate freezing of gait in Parkinson's disease. *Neurosci Lett*. 2016;628:1.
147. Chang WH, Kim MS, Park E, Cho JW, Youn J, Kim YK, et al. Effect of dual-mode and dual-site noninvasive brain stimulation on freezing of gait in patients with Parkinson disease. *Arch Phys Med Rehabil*. 2017;98(7):1283–90.
148. Rektorova I, Sedlackova S, Telecka S, Hlubocky A, Rektor I. Repetitive transcranial stimulation for freezing of gait in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*. 2007;22(10):1518–9.
149. Kim MS, Chang WH, Cho JW, Youn J, Kim YK, Kim SW, et al. Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. *Restor Neurol Neurosci*. 2015;33(4):521–30.
150. Valentino F, Cosentino G, Brighina F, Pozzi NG, Sandrini G, Fierro B, et al. Transcranial direct current stimulation for treatment of freezing of gait: a cross-over study. *Mov Disord*. 2014;29(8):1064–9.
151. Dagan M, Herman T, Harrison R, Zhou J, Giladi N, Ruffini G, et al. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. *Mov Disord*. 2018;33(4):642–6.



# Falls in Older Adults with MCI and Alzheimer's Disease

# 12

Gilles Allali and Joe Verghese

## Introduction

Falls affect around 30% of community-dwelling older adults [1]; older adults with dementia are 2–3 times more likely to fall than non-demented older adults [2]. Falls-related complications increase with advancing age, especially in nursing home residents: 10–25% of falls in nursing home residents result in fractures [3]. The consequences of falls may be severe and include social isolation, hospitalization, mobility disability or death; among older adults admitted to the hospital for falls, half will die in the following year [3]. The morbidity and the mortality associated with falls accounts for 1–2% of the overall health-care expenditures in high-income countries [4]. In 2012, 24,190 older adults died from falls in the United States, while an estimated 3.2 million Americans experienced non-fatal fall injuries in the same year [5]. Fatal falls were estimated in 2015 to cost \$637.2 million in the United States and the treatment of non-fatal fall injury was estimated to cost \$31.3 billion [5].

The type and nature of cognitive impairment impact on fall risks in aging. Older adults with non-Alzheimer's disease (AD) have an increased prevalence of falls than AD patients [6–8]. Multiple falls were reported to occur in 37% of patients

---

G. Allali (✉)

Department of Neurology, Division of Cognitive & Motor Aging, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

Department of Clinical Neurosciences, Geneva University Hospitals and University of Geneva, Geneva, Switzerland

e-mail: [Gilles.Allali@hcuge.ch](mailto:Gilles.Allali@hcuge.ch)

J. Verghese

Department of Neurology, Division of Cognitive & Motor Aging, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA

e-mail: [joe.verghese@einstein.yu.edu](mailto:joe.verghese@einstein.yu.edu)



with dementia with Lewy bodies (DLB) identified using daily fall diaries over a 3-month period, while they occurred in only 6% of AD patients from the same case register [7]. DLB patients had more fall-related injuries than AD patients: 10.7% in DLB versus 1.1% in AD patients in an in-patient Japanese dementia series [8]. Mild cognitive impairment (MCI) has been reported to be associated with both increased [9, 10] and similar [6] risk of falling in comparison to older adults with intact cognition. This discrepancy in terms of fall prevalence in MCI may be explained by the subtype of MCI (amnesic versus non-amnesic forms) included in the different studies and the adjustment on various covariates. Another transitional state between normal aging and dementia – the motoric cognitive risk syndrome (MCR) – that combines slow gait and cognitive complaints [11] – has been associated with an increased risk of falls in five longitudinal aging studies, including over 6000 non-demented older adults [12].

In this chapter, we will focus on the importance of the identification of risk factors for falls, especially those seen in patients with cognitive impairment (1), and clinical methods to assess older adults at risk for falls (2). Then, we will review different approaches to reduce the risk of falling in older adults with poor cognition (3), and finally, we will propose an algorithm for helping clinicians in their falls management strategy. This chapter is not a systematic review of the literature but a comprehensive approach that aims to describe the current practice of the management of falls in older adults with MCI and Alzheimer's disease.

---

## **Risk Factors for Falls in Older Adults with MCI and Alzheimer's Disease**

Falls in aging rarely result from a single risk factor, but from the interaction and the combination of different contributors [13]. For example, the use of a cane or a walker has been associated with falls in some previous studies [14], but this association is more likely related to the inappropriate use of such assistive devices due to impaired executive function that leads to falls. Risk factors for falls have been largely studied in aging (Table 12.1) and include demographics, the integrity of different physiological systems (i.e. neurological, cardiovascular, rheumatologic), the use of specific drugs or environmental hazards [15–17]. The accumulation of different conditions or the occurrence of a unique event, such as a stroke, may predispose to falls. For example, an older patient with a right hemispheric stroke may present with motor deficits, in addition to impaired executive function, neglect, depression and impaired visual field, all of which could act individually or in concert to lead to a fall.

Dementia represents an independent risk factor for falls in older adults [18, 19]. Higher-level gait disorders [20, 21], daytime sleepiness [22], polypharmacy [21], white matter lesions [21] or depression [23] have all been identified as major risk factors for falls in older adults with dementia. Cognitive, behavioural and motor

**Table 12.1** Age-related and Alzheimer's disease/MCI-specific risk factors for falls

Risk factors for falls	
Age-related	AD/MCI specific
<i>Demographic</i>	<i>Demographic</i>
Older age	Older age
Female gender	Female gender
History of falls	History of falls
Sedentariness	Sedentariness
<i>Neurology</i>	<i>Neurological</i>
Neuropathy	Neuropathy
Visual impairment	Visual impairment
Vestibular deficit	Vestibular deficit
Stroke	Stroke
Autonomic dysfunction	Autonomic dysfunction
Mild parkinsonian signs/ parkinsonism	Mild parkinsonian signs/parkinsonism
Gait and balance disorders	Gait and balance disorders
Urinary incontinence	Urinary incontinence
White matter changes	White matter changes
	Cognitive impairment (i.e. executive and visuospatial domains)
	Behavioural disturbances (i.e. agitation)
	Seizures
	Daytime sleepiness
	Loss of independence
<i>Medication and toxic</i>	<i>Medication and toxic</i>
Polypharmacy	Polypharmacy
At-risk drugs (i.e. psychotropic)	At-risk drugs (i.e. neuroleptic, antiepileptic)
Alcohol consumption	Alcohol consumption
<i>Psychiatry</i>	<i>Psychiatry</i>
Depression	Depression
Anxiety	Anxiety
Fear of falling	Fear of falling
<i>Rheumatology</i>	<i>Rheumatology</i>
Osteoporosis	Osteoporosis
Arthritis	Arthritis
Sarcopenia	Sarcopenia
Vitamin D deficiency	Vitamin D deficiency
Feet deformation	Feet deformation
<i>Cardiology</i>	<i>Cardiology</i>
Arrhythmia	Arrhythmia (i.e. bradycardia with cholinesterase inhibitors; QT prolongation with neuroleptics)
<i>Environmental hazards</i>	<i>Environmental hazards</i>

symptoms, in addition to the medications used to treat behavioural disturbances (i.e. psychotropic drugs), are specific risk factors for falls in patients with MCI or AD (Table 12.1). Among the cognitive domains, impairments in executive function [24–27], attention [25, 27], orientation [27] and visuospatial [28] abilities have been associated with falls in older individuals with cognitive impairment. Behavioural symptoms, such as depression, anxiety and fear of falling, have been also associated with falls in community older adults [29]. The relationship between depression and falls is complex, because both depression and use of antidepressants have been associated with falls [30]. Furthermore, in older adults with dementia, it may be difficult to distinguish between depression and apathy that are both frequent and may be seen together or independently. Apathy has been associated with poor gait in older adults with and without dementia [31, 32] and may also contribute to falls.

Motor signs, such as gait and balance impairment or mild parkinsonian signs, are also major contributors to falls in patients with MCI or AD. Increased stride time variability – a marker of cognitive control of gait – has been associated with increased risk of falls in older adults with and without dementia [33–35]. However, the association between high stride time variability and falls has been reported only in demented older adults without AD, but not in AD [6]. Clinical gait abnormalities have been associated with falls in older adults with cognitive impairment: both parkinsonian and frontal gaits are frequently diagnosed in patients with dementia. In comparison to parkinsonian gait, frontal gait is more often associated with falls in older adults without dementia [36]. Among neurological gait abnormalities (i.e. frontal, parkinsonian, unsteady, hemiparetic, neuropathic and spastic), unsteady and neuropathic gaits are the two gait subtypes that predicts the risk of falls in community residing older adults [37]. Mild parkinsonian signs that include gait instability, bradykinesia, rigidity and rest tremor [38] are increased in patients with MCI [39, 40] and dementia [41, 42]. Both cerebrovascular pathologies (i.e. macroscopic, microscopic and arteriolosclerosis) [43] and neuronal loss in the substantia nigra [44] have been associated with mild parkinsonian signs in neuropathological studies. The presence [45] and the worsening [46] of mild parkinsonian signs both predict falls in older adults without Parkinson's disease.

Polypharmacy and specific drug classes, such as psychotropic drugs, are associated with falls in aging [47–49]. In older adults with dementia, the use of benzodiazepines, conventional or atypical neuroleptics, and antidepressants are associated with increased risk of falling [50, 51]. The drug initiation phase represents the highest fall risk period, and higher dosages are associated with increased fall risk [52]. Analgesic and anti-hypertensive drugs are also both contributors to increased risk of falls in individuals with dementia [24]. Regarding anti-dementia drugs, such as cholinesterase inhibitors and memantine, there are conflicting results regarding their association with falls. A retrospective study based on 810 participants included in the Alzheimer's disease Neuroimaging Initiative study concluded that anti-dementia drugs are associated with an increased hazard ratio for falls (adjusted HR = 1.63, CI = [1.24–2.14]) [53]. On the other hand, several reports suggest that both memantine and cholinesterase inhibitors improve gait disorders in older adults with AD [54–60]. Regarding the relationship between falls and cholinesterase inhibitors, a

6-week randomized placebo-controlled study in 23 patients with Parkinson's disease (PD) demonstrated that PD patients fell half as often on donepezil than on placebo [61]. These conflicting results may be explained in part by the increased risk of syncope reported with cholinesterase inhibitors [62], though further research is required to identify specific mechanisms by which cognitive enhancers may increase or decrease risk of falls in this vulnerable population.

Older adults with MCI and Alzheimer's disease share the same risk factors for fall than older adults with intact cognition, in addition to specific risk factors that should be taken into account in the falls prevention.

---

## Clinical Assessment for Falls

Guidelines for assessing falls in older adults with impaired cognitive function are not available, although some recommendations have been proposed for nursing home residents [63]. Medical assessment relies on the clinical examination and interview focusing on the history of falls, fall mechanisms and identification of reversible risk factors such as depression (Table 12.2). Reports from witnesses are key as older adults with impaired cognitive function may have poor recollection of their falls and the surrounding circumstances. A careful interview of the witnesses can reveal specific causes of the fall that may be intrinsic (e.g. seizure, syncope, or drop attack) or extrinsic (e.g. slippery floor). The medications list and the individual comorbid illnesses are also very important in the medical evaluation. Symptoms occurring around the fall incident such as palpitation, chest pain, cough or fever may better target the clinical investigations and prevent expensive and inappropriate tests. Recent changes in treatment, such as introduction of new anti-hypertensive or psychotropic drugs, are important to consider in fallers. Clinical examination with a special emphasis to the neurological assessment will provide information regarding fall contributors and also guide investigations: any signs of head injury, focal neurological signs or parkinsonian signs. Clinical gait examination (i.e. neurological vs. non-neurological gait abnormalities) including standardized tests, such as the quantification of gait speed or the timed up and go test, should also be systematically performed; only neurological gait abnormalities have been associated with increased risk of falling [37]. Including a combined cognitive-motor task such as reciting alternate alphabets while walking (i.e. dual task) is of interest, as dual task-related gait declines have been associated with poor executive and visuospatial abilities in older adults with impaired and intact cognition [64–66]. Furthermore, difficulty in performing walking while talking has been associated with increased risk of falls in community-dwelling older adults [67]. The cognitive assessment should distinguish the presence of delirium from dementia. It should also evaluate for presence of cognitive deficits that are classically associated with increased risk of falling such as executive or visuospatial functions. Bedside cognitive tests, such as orientation, digit span or clock drawing test, should also be performed during the neurological evaluation. Recent behavioural changes, such as the presence of anxiety, depression or fear of falling, should be assessed during the clinical interview, and quantified

**Table 12.2** Clinical assessment for falls in older adults with MCI and Alzheimer's disease

Factors	Assessment
<i>Demographic</i>	Clinical interview focusing on the fall's mechanism (i.e. prodromal signs, reports from witnesses, fall circumstances, asymmetrical weakness, bitten tongue or urinary loss, dizziness)
<i>Neurological</i>	Neurological examination (i.e. Snellen chart, Romberg, deep tendon reflex, parkinsonian signs, pyramidal signs, focal neurological deficits, muscle strength, sensory examination)
	Cognitive assessment (i.e. Mini-Mental State examination, bedside executive, attentional and visuospatial tests)
	Gait assessment (i.e. gait speed, timed up and go test, tandem gait, dual task)
	Orthostatic hypotension testing (immediate and delayed)
	Brain imaging (if traumatic brain injury, focal neurological signs (including prominent gait impairment), delirium, suspicion of normal pressure hydrocephalus)
	Electroencephalogram (if suspicion of seizure or delirium)
	Blood and urinary tests (especially if delirium)
	Chest X-ray (if delirium or fever)
<i>Medication and toxic</i>	Medication list (i.e. special attention to recent change in medication or use of at-risk drug class, such as psychotropic drugs)
	Quantification of alcohol intake
<i>Psychiatry</i>	Clinical interview; short clinical scale (i.e. Hospital Anxiety and Depression Scale, Geriatric Depression Scale)
	Fear of falling assessment (yes/no question)
<i>Rheumatology</i>	Clinical examination (i.e. feet assessment)
	Blood test (i.e. calcium and vitamin D)
	Body mass index
<i>Cardiology</i>	Electrocardiogram (if delirium, chest pain or palpitations)
	Holter monitoring (if palpitation, syncope or focal neurological signs)
<i>Environmental Hazards</i>	Home environment risk evaluation

with brief instrument tools, such as the five-item version of the Geriatric Depression Scale [68] or other screening questionnaires (i.e. Fall Efficacy Scale – International [69] for fear of falling). The relationship between fear of falling and falls is complex: fear of falling may precede or follow the first fall [70]. Furthermore, fear of falling predicts falls only in older individuals with gait and postural instability [71]. The evaluation for orthostatic hypotension – which is frequently asymptomatic in patients with dementia [72] – should be performed by checking blood pressure after 2–5 minutes of quiet standing: a fall of at least 20 mmHg in systolic pressure or at least 10 mmHg in diastolic pressure compared to resting blood pressure values is diagnostic [73].

Standard laboratory investigations, including blood and urinary tests, with complete blood count, serum electrolytes, creatine kinase (i.e. rhabdomyolysis) and

vitamin D levels, should be performed in fallers. Brain imaging should be considered in any fallers with head injury (especially in individuals with antiplatelet or anticoagulant medication), focal neurological signs or delirium. Electroencephalogram should be conducted in fallers with history or suspicion of seizure and in those with delirium in order to exclude a non-convulsive status. Electrocardiogram should be checked in patients with history of cardiomyopathy, palpitation or chest pain; the clinical presentation of acute coronary syndrome is often atypical in older adults (i.e. syncope or pre-syncope manifestation) [74].

---

## Falls Management

Once the aetiologies of fall are identified, appropriate management should be initiated. Some reversible risk factors can be easily treated. For example, low visual acuity can be improved by using prescription eyeglasses; foot deformities may be corrected by an orthopaedist or podiatrist; cardiac arrhythmia related to fall should receive appropriate treatment (i.e. pacemaker or antiarrhythmic drug). In older adults with MCI and AD, behavioural and psychological disturbances that are associated with increased risk of falling should receive special attention; non-pharmacological treatments should be always the first approach. A large number of non-pharmacological interventions have demonstrated their effectiveness for treating behavioural and psychological symptoms in patients with dementia [75–79]. Music therapy or behavioural management techniques reduce these symptoms and, by consequence, may contribute to decrease the risk of falling. Motor symptoms should also be targeted in patients with MCI or Alzheimer's disease: mild parkinsonian signs or parkinsonism by discontinuing neuroleptics or changing anti-epileptic drugs (i.e. valproate) if these are being taken and can be treated with dopaminergic drugs (levodopa/carbidopa or levodopa/benserazide – avoid dopamine agonist in patients with dementia [80]), though they are less likely to show a benefit compared to patients with idiopathic Parkinson's disease. Normal-pressure hydrocephalus can be shunted, bearing in mind that between 20% and 45% of patients with normal pressure hydrocephalus have comorbid AD [81–83], and these patients with comorbid Alzheimer's disease and normal pressure hydrocephalus have an initial good outcome after shunt surgery, although they will experience a later deterioration in comparison to patients with isolated normal pressure hydrocephalus [82, 84, 85]. Orthostatic hypotension, a frequent symptom in patients with dementia (around 50%) [86], can be managed by non-pharmacological measures (i.e. removing offending medications, arising slowly, raising the head of the bed and avoiding large meals) or specific drugs (i.e. fludrocortisone or midodrine). Home hazard modifications should also be included in the falls management strategy, as previous studies have demonstrated the efficacy of home modification that reduces falls by 39% in older adults [87–89].

Cleaning the medication list is a key component of falls prevention, especially in fallers with MCI or AD. Polypharmacy has also been associated with falls in patients with dementia [90]. Although not specifically studied in patients with MCI or AD, the following drug classes have been associated with falls in aging and need special considerations: antiepileptics [47], high dosages of antiparkinsonian drugs [91], opioids [92], nonsteroidal anti-inflammatory drugs [49], diuretics [93] or type 1a anti-arrhythmic drugs [93].

A growing number of non-pharmacological interventions, such as physical therapy or Tai-chi, have been tested for fall prevention in older adults with intact cognition [94–96]. Although cognitive impairment does not represent a major barrier to participation in such interventions, reduced activities of daily living, autonomic disturbances or excessive daytime sleepiness may interfere with the participation of older adults with cognitive impairment [97]. However, the feasibility of exercise interventions has been demonstrated in people with MCI and with dementia [98], even in the more advanced stages [99]. Different non-pharmacological interventions aiming to reduce falls or related fear of falling have been tested in older adults with MCI and dementia. Specific non-pharmacological interventions to prevent falls will be discussed in detail in Section IV of this book, but in this chapter, we will summarize the trials specifically targeting MCI and AD (Table 12.3) [100–108]. The interventions incorporate a variety of activities (i.e. balance or walking exercises, video game) as well as cognitive training provided at home or in day-care centres. These interventions included both community-dwellers and older adults residing in nursing homes. The frequencies of these interventions have ranged from 2 to 5 sessions per week for 2–12 months. The duration of individual sessions ranged from 30 to 60 minutes. Falls and fear of falling usually are not the main outcomes of these interventions. These interventions have demonstrated that physical activity interventions reduce the incident falls and risk of falling. However, there is a need for large randomized controlled trials with falls as the main outcome that include participants with Alzheimer's disease and non-AD dementia.

Advanced technologies will also contribute to improve the fall risk management in older adults with cognitive decline. New tools, such as the use of accelerometers during everyday activities [109], electronic clinical reminders [110], or smart home systems [111, 112], have been tested in older adults and need to be adapted for individuals with cognitive impairment.

The various non-pharmacological interventions listed in Table 12.3 that include different forms of individual or combined physical therapies (i.e. balance or walking exercises) highlight the key role of physical therapists in falls prevention in older adults with MCI or AD. The growing number of advanced technologies available for reducing falls combined to the demonstrated roles of environmental modification and training in activity of daily living also indicates the importance of including occupational therapy practitioners for reducing risk of falls in patients with MCI or AD.



**Table 12.3** Non-pharmacological interventions in older adults with MCI or Alzheimer's disease with falls or concern of falling as an outcome

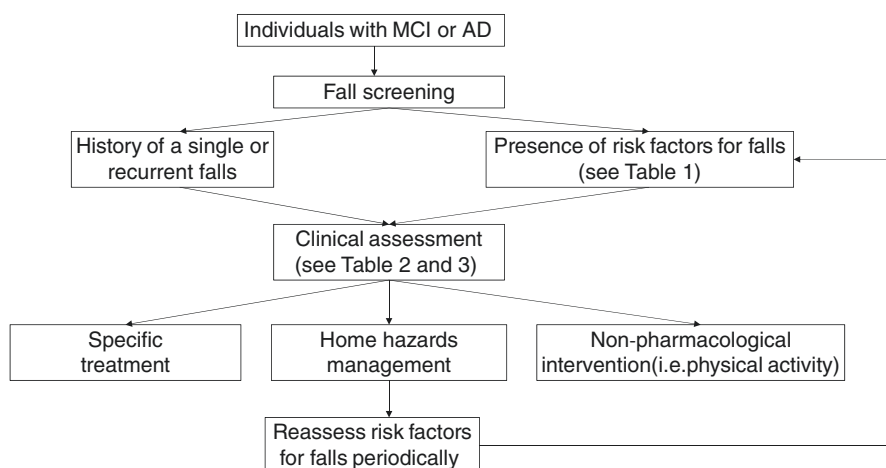
Study	Population/setting	Study design/outcomes	Type of intervention	Duration of intervention	Main results
Sungkarat, 2017 Thailand	66 MCI (MMSE: $26.2 \pm 2.0$ )/community dwellers/home and centre based	Randomized controlled trial/fall risk score (secondary outcome)	Tai Chi (centre based and home based) versus control group receiving educational material related to cognition and fall	50 min/3 times per week/15 weeks (3 weeks centre based and 12 weeks home based)	Reduction in the fall risk score (Physiological Profile Assessment) in the Tai Chi group in comparison to the control group
Padala, 2017 USA	30 AD (MMSE: $22.9 \pm 2.2$ )/community dwellers/home based/control group	Randomized controlled trial/Fear of falling (secondary outcome)	Wii-Fit interactive videogame-led physical exercise program versus control group doing walking program	30 min/5 times per week/8 weeks	Reduction in fear of falling (Fall Efficacy Scale) in the Wii-Fit interactive videogame-led physical exercise program group in comparison to the control group
Taylor, 2017 Australia	42 participants with dementia (MMSE: $21.2 \pm 4.1$ )/community dweller/no control group	Uncontrolled trial/concern about falling (secondary outcome)	Individually tailored exercise program	6 months home based	Reduction in concern about falling
Hagovská, 2016 Slovak Republic	80 MCI (MMSE: $26.0 \pm 2.0$ )/community dwellers/outpatients clinic/control group	Randomized controlled trial/fear of falling (secondary outcome)	Cognitive and balance training versus control group receiving only balance training	60 min/twice per week/10 weeks	No difference after training for fear of falling between both groups
Cadore, 2014 Spain	18 participants with 10 AD, 1 VD and 7 mixed dementia (MMSE: $15.1 \pm 6.3$ )/nursing home/no control group	Uncontrolled trial/incident falls (secondary outcome)	Multicomponent exercise program (walking, balance, cognitive exercises)	8 weeks (4 weeks of exercise training +4 weeks of resistance training)	Decreased incidence of fall

(continued)

**Table 12.3** (continued)

Study	Population/setting	Study design/ outcomes	Type of intervention	Duration of intervention	Main results
Wesson, 2013 Australia	22 participants with dementia (MMSE: 23.5 ± 3.7)/community dwellers/control group consisted of usual care	Randomized controlled trial (pilot study)/fear of falling and falls calendar (secondary outcomes)	Home-based physical and balance training exercises and home hazard reduction	12 weeks	Falls reduction in the intervention group.
Pitkala, 2013 Finland	210 AD (MMSE: 17.7 ± 6.6)/community dwellers/home-based exercise versus group-based exercise versus control group consisting of educational advice on nutrition and exercise	Randomized controlled trial/ number of falls (secondary outcome)	Individualized multicomponent exercise	60 min/twice per week/12 months	Reduction of number of falls in the intervention groups but no changes in incidence of fractures or hospitalization
Yoon, 2013 Korea	30 demented participants (MMSE: 18.0 ± 1.5)/long term care facility/cognitive activity with physical exercise versus cognitive activity only	Randomized controlled trial/fear of falling (secondary outcome)	Cognitive activity combined with physical exercise	30 min/3 times per week/12 weeks	Reduction of fear of falling in the combined cognitive activity with physical exercise group in comparison to the cognitive activity only group
Suttanon, 2012 Australia	40 AD (MMSE: 20.9 ± 4.7)/ community dwellers/control group consisted of educational sessions on dementia and aging)	Randomized controlled trial/falls risk (secondary outcome)	Multicomponent home- based exercise (balance, strength, walking)	5 per week/6 months	Reduction for the falls risk for older people – community score in the intervention group

*MCI* mild cognitive impairment, *AD* Alzheimer's disease, *VD* vascular dementia, *MMSE* Mini-Mental State Examination



**Fig. 12.1** Algorithm for falls management strategy in older adults with MCI or Alzheimer's disease. Individuals with MCI or Alzheimer's disease (AD) present specific risk factors for falls (i.e. cognitive, behavioural or motor impairments) in addition to the same risk factors found in individuals with intact cognition (i.e. rheumatologic or cardiologic conditions). The management of falls can rely on the implementation of various interventions (i.e. cleaning the medication list, treating a cardiac arrhythmia, home hazards management, physical activity program). Then, the clinician should periodically adapt these interventions depending on the patient adherence and/or the appearance of new risk factors for falls

## Conclusion

Older adults with MCI or Alzheimer's disease are at increased risk of falls than individuals with intact cognition and should be systematically screened for history or risk factors of falls. In Fig. 12.1, we propose an algorithm that may help clinicians to manage elderly fallers with MCI or Alzheimer's disease. The screening strategy should also include identification of the specific risk factors found in these individuals (i.e. cognitive, behavioural or motor impairments). Then, the management of falls risk will rely on multifactorial approaches that range from cleaning the medication list to physical activity program. These risk factors should be regularly reassessed as Alzheimer's disease is a progressive chronic condition associated with the appearance of evolving cognitive, behavioural and motor decline.

## References

1. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology*. 2010;21(5):658–68. <https://doi.org/10.1097/EDE.0b013e3181e89905>.
2. Eriksson S, Strandberg S, Gustafson Y, Lundin-Olsson L. Circumstances surrounding falls in patients with dementia in a psychogeriatric ward. *Arch Gerontol Geriatr*. 2009;49(1):80–7. <https://doi.org/10.1016/j.archger.2008.05.005>.

3. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age Ageing*. 2006;35(Suppl 2):ii37–41. <https://doi.org/10.1093/ageing/af084>.
4. Heinrich S, Rapp K, Rissmann U, Becker C, König HH. Cost of falls in old age: a systematic review. *Osteoporos Int*. 2010;21(6):891–902. <https://doi.org/10.1007/s00198-009-1100-1>.
5. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults - United States. *J Saf Res*. 2016;58:99–103. <https://doi.org/10.1016/j.jsr.2016.05.001>.
6. Allali G, Launay CP, Blumen HM, Callisaya ML, De Cock AM, Kressig RW, Srikanth V, Steinmetz JP, Verghese J, Beauchet O, Biomathics C. Falls, cognitive impairment, and gait performance: results from the GOOD initiative. *J Am Med Dir Assoc*. 2017c;18(4):335–40. <https://doi.org/10.1016/j.jamda.2016.10.008>.
7. Ballard CG, Shaw F, Lowery K, McKeith I, Kenny R. The prevalence, assessment and associations of falls in dementia with Lewy bodies and Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1999;10(2):97–103. <https://doi.org/10.1159/000017108>.
8. Imamura T, Hirono N, Hashimoto M, Kazui H, Tanimukai S, Hanihara T, Takahara A, Mori E. Fall-related injuries in dementia with Lewy bodies (DLB) and Alzheimer's disease. *Eur J Neurol*. 2000;7(1):77–9.
9. Borges Sde M, Radanovic M, Forlenza OV. Fear of falling and falls in older adults with mild cognitive impairment and Alzheimer's disease. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2015;22(3):312–21. <https://doi.org/10.1080/13825585.2014.933770>.
10. Tyrovolas S, Koyanagi A, Lara E, Santini ZI, Haro JM. Mild cognitive impairment is associated with falls among older adults: findings from the Irish Longitudinal Study on Ageing (TILDA). *Exp Gerontol*. 2016;75:42–7. <https://doi.org/10.1016/j.exger.2015.12.008>.
11. Verghese J, Wang C, Lipton RB, Holtzer R. Motoric cognitive risk syndrome and the risk of dementia. *J Gerontol A Biol Sci Med Sci*. 2013;68(4):412–8. <https://doi.org/10.1093/gerona/gls191>.
12. Callisaya ML, Ayers E, Barzilai N, Ferrucci L, Guralnik JM, Lipton RB, Otahal P, Srikanth VK, Verghese J. Motoric cognitive risk syndrome and falls risk: a multi-center study. *J Alzheimers Dis*. 2016;53(3):1043–52. <https://doi.org/10.3233/JAD-160230>.
13. Thurman DJ, Stevens JA, Rao JK, Quality Standards Subcommittee of the American Academy of N. Practice parameter: assessing patients in a neurology practice for risk of falls (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(6):473–9. <https://doi.org/10.1212/01.wnl.0000299085.18976.20>.
14. Bateni H, Maki BE. Assistive devices for balance and mobility: benefits, demands, and adverse consequences. *Arch Phys Med Rehabil*. 2005;86(1):134–45.
15. Australian commission on safety and quality in health care. Falls Prevention. Accessed 6th March 2017.
16. National Institute for Clinical Excellence. Falls in older people: assessing risk and prevention. Accessed 6th March 2017.
17. Panel on Prevention of Falls in Older Persons AGS, British Geriatrics S. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc*. 2011;59(1):148–57. <https://doi.org/10.1111/j.1532-5415.2010.03234.x>.
18. Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. *JAMA*. 1987;257(11):1492–5.
19. van Doorn C, Gruber-Baldini AL, Zimmerman S, Hebel JR, Port CL, Baumgarten M, Quinn CC, Taler G, May C, Magaziner J. Epidemiology of Dementia in Nursing Homes Research G. Dementia as a risk factor for falls and fall injuries among nursing home residents. *J Am Geriatr Soc*. 2003;51(9):1213–8.
20. Eshkoor SA, Hamid TA, Nudin SS, Mun CY. A research on functional status, environmental conditions, and risk of falls in dementia. *Int J Alzheimers Dis*. 2014;2014:769062. <https://doi.org/10.1155/2014/769062>.

21. Ogama N, Sakurai T, Shimizu A, Toba K. Regional white matter lesions predict falls in patients with amnesic mild cognitive impairment and Alzheimer's disease. *J Am Med Dir Assoc.* 2014;15(1):36–41. <https://doi.org/10.1016/j.jamda.2013.11.004>.
22. Chen PY, Chiu HT, Chiu HY. Daytime sleepiness is independently associated with falls in older adults with dementia. *Geriatr Gerontol Int.* 2016;16(7):850–5. <https://doi.org/10.1111/ggi.12567>.
23. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. *PLoS One.* 2009;4(5):e5521. <https://doi.org/10.1371/journal.pone.0005521>.
24. Kosse NM, de Groot MH, Vuilleme N, Hortobagyi T, Lamoth CJ. Factors related to the high fall rate in long-term care residents with dementia. *Int Psychogeriatr.* 2015;27(5):803–14. <https://doi.org/10.1017/S104161021400249X>.
25. Mirelman A, Herman T, Brozgov M, Dorfman M, Sprecher E, Schweiger A, Giladi N, Hausdorff JM. Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. *PLoS One.* 2012;7(6):e40297. <https://doi.org/10.1371/journal.pone.0040297>.
26. Muir SW, Berg K, Chesworth B, Speechley M. Use of the Berg Balance Scale for predicting multiple falls in community-dwelling elderly people: a prospective study. *Phys Ther.* 2008;88(4):449–59. <https://doi.org/10.2522/ptj.20070251>.
27. Whitney J, Close JC, Jackson SH, Lord SR. Understanding risk of falls in people with cognitive impairment living in residential care. *J Am Med Dir Assoc.* 2012;13(6):535–40. <https://doi.org/10.1016/j.jamda.2012.03.009>.
28. Ansai JH, de Andrade LP, Masse FAA, Goncalves J, de Medeiros Takahashi AC, Vale FAC, Rebelatto JR. Risk factors for falls in older adults with mild cognitive impairment and mild Alzheimer disease. *J Geriatr Phys Ther.* 2017;1. <https://doi.org/10.1519/JPT.0000000000000135>.
29. Taylor ME, Delbaere K, Lord SR, Mikolaizak AS, Brodaty H, Close JC. Neuropsychological, physical, and functional mobility measures associated with falls in cognitively impaired older adults. *J Gerontol A Biol Sci Med Sci.* 2014;69(8):987–95. <https://doi.org/10.1093/geronol/glt166>.
30. Kvelde T, Lord SR, Close JC, Reppermund S, Kochan NA, Sachdev P, Brodaty H, Delbaere K. Depressive symptoms increase fall risk in older people, independent of antidepressant use, and reduced executive and physical functioning. *Arch Gerontol Geriatr.* 2015;60(1):190–5. <https://doi.org/10.1016/j.archger.2014.09.003>.
31. Allali G, Laidet M, Armand S, Saj A, Krack P, Assal F. Apathy and higher level of gait control in normal pressure hydrocephalus. *Int J Psychophysiol.* 2017b;119:127–31. <https://doi.org/10.1016/j.ijpsycho.2016.12.002>.
32. Ayers E, Shapiro M, Holtzer R, Barzilai N, Milman S, Verghese J. Symptoms of apathy independently predict incident frailty and disability in community-dwelling older adults. *J Clin Psychiatry.* 2017;78(5):e529–36. <https://doi.org/10.4088/JCP.15m10113>.
33. Hausdorff JM. Gait variability: methods, modeling and meaning. *J Neuroeng Rehabil.* 2005;2:19. <https://doi.org/10.1186/1743-0003-2-19>.
34. Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of executive function on locomotor function: divided attention increases gait variability in Alzheimer's disease. *J Am Geriatr Soc.* 2003;51(11):1633–7.
35. Sterke CS, van Beeck EF, Looman CW, Kressig RW, van der Cammen TJ. An electronic walkway can predict short-term fall risk in nursing home residents with dementia. *Gait Posture.* 2012;36(1):95–101. <https://doi.org/10.1016/j.gaitpost.2012.01.012>.
36. Ambrose A, Levalley A, Verghese J. A comparison of community-residing older adults with frontal and parkinsonian gaits. *J Neurol Sci.* 2006;248(1–2):215–8. <https://doi.org/10.1016/j.jns.2006.05.035>.
37. Verghese J, Ambrose AF, Lipton RB, Wang C. Neurological gait abnormalities and risk of falls in older adults. *J Neurol.* 2010;257(3):392–8. <https://doi.org/10.1007/s00415-009-5332-y>.

38. Louis ED, Bennett DA. Mild Parkinsonian signs: an overview of an emerging concept. *Mov Disord.* 2007;22(12):1681–8. <https://doi.org/10.1002/mds.21433>.
39. Boyle PA, Wilson RS, Aggarwal NT, Arvanitakis Z, Kelly J, Bienias JL, Bennett DA. Parkinsonian signs in subjects with mild cognitive impairment. *Neurology.* 2005;65(12):1901–6. <https://doi.org/10.1212/01.wnl.0000188878.81385.73>.
40. Louis ED, Schupf N, Manly J, Marder K, Tang MX, Mayeux R. Association between mild parkinsonian signs and mild cognitive impairment in a community. *Neurology.* 2005;64(7):1157–61. <https://doi.org/10.1212/01.WNL.0000156157.97411.5E>.
41. Richards M, Stern Y, Mayeux R. Subtle extrapyramidal signs can predict the development of dementia in elderly individuals. *Neurology.* 1993;43(11):2184–8.
42. Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Parkinsonianlike signs and risk of incident Alzheimer disease in older persons. *Arch Neurol.* 2003;60(4):539–44. <https://doi.org/10.1001/archneur.60.4.539>.
43. Buchman AS, Leurgans SE, Nag S, Bennett DA, Schneider JA. Cerebrovascular disease pathology and parkinsonian signs in old age. *Stroke.* 2011;42(11):3183–9. <https://doi.org/10.1161/STROKEAHA.111.623462>.
44. Buchman AS, Shulman JM, Nag S, Leurgans SE, Arnold SE, Morris MC, Schneider JA, Bennett DA. Nigral pathology and parkinsonian signs in elders without Parkinson disease. *Ann Neurol.* 2012;71(2):258–66. <https://doi.org/10.1002/ana.22588>.
45. Dahodwala N, Nwadiogbu C, Fitts W, Partridge H, Karlawish J. Parkinsonian signs are a risk factor for falls. *Gait Posture.* 2017;55:1–5. <https://doi.org/10.1016/j.gaitpost.2017.03.039>.
46. Buracchio T, Arvanitakis Z, Leurgans S, Bennett DA. Parkinsonian signs and incident falls in older persons without Parkinson's disease. *J Am Geriatr Soc.* 2010;58(1):205–6. <https://doi.org/10.1111/j.1532-5415.2009.02657.x>.
47. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, Schwartz AV, Hanlon JT, Nevitt MC, Study of Osteoporotic Fractures Research G. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc.* 2002;50(10):1629–37.
48. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. psychotropic drugs. *J Am Geriatr Soc.* 1999a;47(1):30–9.
49. Woolcott JC, Richardson KJ, Wiens MO, Patel B, Marin J, Khan KM, Marra CA. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* 2009;169(21):1952–60. <https://doi.org/10.1001/archinternmed.2009.357>.
50. Bueno-Cavanillas A, Padilla-Ruiz F, Jimenez-Moleon JJ, Peinado-Alonso CA, Galvez-Vargas R. Risk factors in falls among the elderly according to extrinsic and intrinsic precipitating causes. *Eur J Epidemiol.* 2000;16(9):849–59.
51. Liperoti R, Onder G, Lapane KL, Mor V, Friedman JH, Bernabei R, Gambassi G. Conventional or atypical antipsychotics and the risk of femur fracture among elderly patients: results of a case-control study. *J Clin Psychiatry.* 2007;68(6):929–34.
52. Bozat-Emre S, Doupe M, Kozyrskyj AL, Grymonpre R, Mahmud SM. Atypical antipsychotic drug use and falls among nursing home residents in Winnipeg, Canada. *Int J Geriatr Psychiatry.* 2015;30(8):842–50. <https://doi.org/10.1002/gps.4223>.
53. Epstein NU, Guo R, Farlow MR, Singh JP, Fisher M. Medication for Alzheimer's disease and associated fall hazard: a retrospective cohort study from the Alzheimer's disease neuroimaging initiative. *Drugs Aging.* 2014;31(2):125–9. <https://doi.org/10.1007/s40266-013-0143-3>.
54. Assal F, Allali G, Kressig RW, Herrmann FR, Beauchet O. Galantamine improves gait performance in patients with Alzheimer's disease. *J Am Geriatr Soc.* 2008;56(5):946–7. <https://doi.org/10.1111/j.1532-5415.2008.01657.x>.
55. Beauchet O, Allali G, Launay C, Fantino B, Annweiler C. Does memantine improve the gait of individuals with Alzheimer's disease? *J Am Geriatr Soc.* 2011;59(11):2181–2. <https://doi.org/10.1111/j.1532-5415.2011.03648.x>.
56. Beauchet O, Launay CP, Allali G, Annweiler C. Changes in gait variability with anti-dementia drugs: a systematic review and meta-analysis. *CNS Drugs.* 2014a;28(6):513–8. <https://doi.org/10.1007/s40263-014-0170-6>.

57. Beauchet O, Launay CP, Allali G, Herrmann FR, Annweiler C. Gait changes with anti-dementia drugs: a prospective, open-label study combining single and dual task assessments in patients with Alzheimer's disease. *Drugs Aging*. 2014b;31(5):363–72. <https://doi.org/10.1007/s40266-014-0175-3>.
58. Beauchet O, Launay CP, Montero-Odasso M, Annweiler C, Allali G. Anti-dementia drugs-related changes in gait performance while single and dual tasking in patients with Alzheimer disease: a meta-analysis. *Curr Alzheimer Res*. 2015;12(8):761–71.
59. Montero-Odasso M, Muir-Hunter SW, Oteng-Amoako A, Gopaul K, Islam A, Borrie M, Wells J, Speechley M. Donepezil improves gait performance in older adults with mild Alzheimer's disease: a phase II clinical trial. *J Alzheimers Dis*. 2015;43(1):193–9. <https://doi.org/10.3233/JAD-140759>.
60. Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. *J Am Geriatr Soc*. 2009;57(2):359–60. <https://doi.org/10.1111/j.1532-5415.2009.02085.x>.
61. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. *Neurology*. 2010;75(14):1263–9. <https://doi.org/10.1212/WNL.0b013e3181f6128c>.
62. Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. *J Am Geriatr Soc*. 2011;59(6):1019–31. <https://doi.org/10.1111/j.1532-5415.2011.03450.x>.
63. Neyens JC, Dijkcs BP, van Haastregt JC, de Witte LP, van den Heuvel WJ, Crebolder HF, Schols JM. The development of a multidisciplinary fall risk evaluation tool for demented nursing home patients in the Netherlands. *BMC Public Health*. 2006;6:74. <https://doi.org/10.1186/1471-2458-6-74>.
64. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60(11):2127–36. <https://doi.org/10.1111/j.1532-5415.2012.04209.x>.
65. Nankar M, Szturm T, Marotta J, Shay B, Beauchet O, Allali G. The interacting effects of treadmill walking and different types of visuospatial cognitive task: discriminating dual task and age effects. *Arch Gerontol Geriatr*. 2017;73:50–9. <https://doi.org/10.1016/j.archger.2017.07.013>.
66. Yogeve-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329–42; quiz 472. <https://doi.org/10.1002/mds.21720>.
67. Ayers EI, Tow AC, Holtzer R, Verghese J. Walking while talking and falls in aging. *Gerontology*. 2014;60(2):108–13. <https://doi.org/10.1159/000355119>.
68. Hoyl MT, Alessi CA, Harker JO, Josephson KR, Pietruszka FM, Koelfgen M, Mervis JR, Fitten LJ, Rubenstein LZ. Development and testing of a five-item version of the geriatric depression scale. *J Am Geriatr Soc*. 1999;47(7):873–8.
69. Yardley L, Beyer N, Hauer K, Kempen G, Piot-Ziegler C, Todd C. Development and initial validation of the falls efficacy scale-international (FES-I). *Age Ageing*. 2005;34(6):614–9. <https://doi.org/10.1093/ageing/afi196>.
70. Friedman SM, Munoz B, West SK, Rubin GS, Fried LP. Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. *J Am Geriatr Soc*. 2002;50(8):1329–35.
71. Allali G, Ayers EI, Holtzer R, Verghese J. The role of postural instability/gait difficulty and fear of falling in predicting falls in non-demented older adults. *Arch Gerontol Geriatr*. 2017a;69:15–20. <https://doi.org/10.1016/j.archger.2016.09.008>.
72. Bengtsson-Lindberg M, Larsson V, Minthon L, Wattmo C, Londo E. Lack of orthostatic symptoms in dementia patients with orthostatic hypotension. *Clin Auton Res*. 2015;25(2):87–94. <https://doi.org/10.1007/s10286-014-0244-z>.
73. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz I, Schondorff R, Stewart JM, van Dijk JG. Consensus statement on the



- definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res*. 2011;21(2):69–72. <https://doi.org/10.1007/s10286-011-0119-5>.
74. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G, Investigators G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the global registry of acute coronary events. *Chest*. 2004;126(2):461–9. <https://doi.org/10.1378/chest.126.2.461>.
  75. Abraha I, Rimland JM, Trotta FM, Dell'Aquila G, Cruz-Jentoft A, Petrovic M, Gudmundsson A, Soiza R, O'Mahony D, Guaita A, Cherubini A. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open*. 2017;7(3):e012759. <https://doi.org/10.1136/bmjopen-2016-012759>.
  76. de Oliveira AM, Radanovic M, de Mello PC, Buchain PC, Vizzotto AD, Celestino DL, Stella F, Piersol CV, Forlenza OV. Nonpharmacological interventions to reduce behavioral and psychological symptoms of dementia: a systematic review. *Biomed Res Int*. 2015;2015:218980. <https://doi.org/10.1155/2015/218980>.
  77. Deudon A, Maubourguet N, Gervais X, Leone E, Brocker P, Carcaillon L, Riff S, Lavallart B, Robert PH. Non-pharmacological management of behavioural symptoms in nursing homes. *Int J Geriatr Psychiatry*. 2009;24(12):1386–95. <https://doi.org/10.1002/gps.2275>.
  78. Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S, Patel N, Omar RZ, Katona C, Cooper C. Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. *Br J Psychiatry*. 2014;205(6):436–42. <https://doi.org/10.1192/bjp.bp.113.141119>.
  79. Narme P, Clement S, Ehrle N, Schiaratura L, Vachez S, Courtaigne B, Munsch F, Samson S. Efficacy of musical interventions in dementia: evidence from a randomized controlled trial. *J Alzheimers Dis*. 2014;38(2):359–69. <https://doi.org/10.3233/JAD-130893>.
  80. Marras C, Lang A. Invited article: changing concepts in Parkinson disease: moving beyond the decade of the brain. *Neurology*. 2008;70(21):1996–2003. <https://doi.org/10.1212/01.wnl.0000312515.52545.51>.
  81. Bech-Azeddine R, Hogh P, Juhler M, Gjerris F, Waldemar G. Idiopathic normal-pressure hydrocephalus: clinical comorbidity correlated with cerebral biopsy findings and outcome of cerebrospinal fluid shunting. *J Neurol Neurosurg Psychiatry*. 2007;78(2):157–61. <https://doi.org/10.1136/jnnp.2006.095117>.
  82. Pomeraniec IJ, Bond AE, Lopes MB, Jane JA Sr. Concurrent Alzheimer's pathology in patients with clinical normal pressure hydrocephalus: correlation of high-volume lumbar puncture results, cortical brain biopsies, and outcomes. *J Neurosurg*. 2016;124(2):382–8. <https://doi.org/10.3171/2015.2.JNS142318>.
  83. Savolainen S, Paljarvi L, Vapalahti M. Prevalence of Alzheimer's disease in patients investigated for presumed normal pressure hydrocephalus: a clinical and neuropathological study. *Acta Neurochir*. 1999;141(8):849–53.
  84. Craven CL, Baudracco I, Zetterberg H, Lunn MPT, Chapman MD, Lakdawala N, Watkins LD, Toma AK. The predictive value of T-tau and Aβ1–42 levels in idiopathic normal pressure hydrocephalus. *Acta Neurochir*. 2017;159(12):2293–300. <https://doi.org/10.1007/s00701-017-3314-x>.
  85. Yasar S, Jusue-Torres I, Lu J, Robison J, Patel MA, Crain B, Carson KA, Hoffberger J, Batra S, Sankey E, Moghekar A, Rigamonti D. Alzheimer's disease pathology and shunt surgery outcome in normal pressure hydrocephalus. *PLoS One*. 2017;12(8):e0182288. <https://doi.org/10.1371/journal.pone.0182288>.
  86. Freidenberg DL, Shaffer LE, Macalester S, Fannin EA. Orthostatic hypotension in patients with dementia: clinical features and response to treatment. *Cogn Behav Neurol*. 2013;26(3):105–20. <https://doi.org/10.1097/WNN.0000000000000003>.
  87. Carter SE, Campbell EM, Sanson-Fisher RW, Redman S, Gillespie WJ. Environmental hazards in the homes of older people. *Age Ageing*. 1997;26(3):195–202.

88. Nikolaus T, Bach M. Preventing falls in community-dwelling frail older people using a home intervention team (HIT): results from the randomized falls-HIT trial. *J Am Geriatr Soc.* 2003;51(3):300–5.
89. Stevens M, Holman CD, Bennett N. Preventing falls in older people: impact of an intervention to reduce environmental hazards in the home. *J Am Geriatr Soc.* 2001;49(11):1442–7.
90. Sterke CS, Verhagen AP, van Beeck EF, van der Cammen TJ. The influence of drug use on fall incidents among nursing home residents: a systematic review. *Int Psychogeriatr.* 2008;20(5):890–910. <https://doi.org/10.1017/S104161020800714X>.
91. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with parkinsonism and anti-Parkinson drugs. *Calcif Tissue Int.* 2007;81(3):153–61. <https://doi.org/10.1007/s00223-007-9065-6>.
92. Takkouche B, Montes-Martinez A, Gill SS, Etminan M. Psychotropic medications and the risk of fracture: a meta-analysis. *Drug Saf.* 2007;30(2):171–84.
93. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: II. Cardiac and analgesic drugs. *J Am Geriatr Soc.* 1999b;47(1):40–50.
94. Fernandez-Arguelles EL, Rodriguez-Mansilla J, Antunez LE, Garrido-Ardila EM, Munoz RP. Effects of dancing on the risk of falling related factors of healthy older adults: a systematic review. *Arch Gerontol Geriatr.* 2015;60(1):1–8. <https://doi.org/10.1016/j.archger.2014.10.003>.
95. Rose DJ, Hernandez D. The role of exercise in fall prevention for older adults. *Clin Geriatr Med.* 2010;26(4):607–31. <https://doi.org/10.1016/j.cger.2010.07.003>.
96. Stubbs B, Brefka S, Denking MD. What works to prevent falls in community-dwelling older adults? Umbrella review of meta-analyses of randomized controlled trials. *Phys Ther.* 2015;95(8):1095–110. <https://doi.org/10.2522/ptj.20140461>.
97. Stubbs B, Eggermont L, Soundy A, Probst M, Vandenbulcke M, Vancampfort D. What are the factors associated with physical activity (PA) participation in community dwelling adults with dementia? A systematic review of PA correlates. *Arch Gerontol Geriatr.* 2014;59(2):195–203. <https://doi.org/10.1016/j.archger.2014.06.006>.
98. Allali G, Verghese J. Management of Gait Changes and Fall Risk in MCI and dementia. *Curr Treat Options Neurol.* 2017;19(9):29. <https://doi.org/10.1007/s11940-017-0466-1>.
99. Cott CA, Dawson P, Sidani S, Wells D. The effects of a walking/talking program on communication, ambulation, and functional status in residents with Alzheimer disease. *Alzheimer Dis Assoc Disord.* 2002;16(2):81–7.
100. Cadore EL, Moneo AB, Mensat MM, Munoz AR, Casas-Herrero A, Rodriguez-Manas L, Izquierdo M. Positive effects of resistance training in frail elderly patients with dementia after long-term physical restraint. *Age.* 2014;36(2):801–11. <https://doi.org/10.1007/s11357-013-9599-7>.
101. Hagovska M, Olekszyova Z. Impact of the combination of cognitive and balance training on gait, fear and risk of falling and quality of life in seniors with mild cognitive impairment. *Geriatr Gerontol Int.* 2016;16(9):1043–50. <https://doi.org/10.1111/ggi.12593>.
102. Padala KP, Padala PR, Lensing SY, Dennis RA, Bopp MM, Roberson PK, Sullivan DH. Home-based exercise program improves balance and fear of falling in community-dwelling older adults with mild Alzheimer's disease: a pilot study. *J Alzheimer's Dis.* 2017;59(2):565–74. <https://doi.org/10.3233/JAD-170120>.
103. Pitkala KH, Poysti MM, Laakkonen ML, Tilvis RS, Savikko N, Kautiainen H, Strandberg TE. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. *JAMA Intern Med.* 2013;173(10):894–901. <https://doi.org/10.1001/jamainternmed.2013.359>.
104. Sungkarat S, Boripuntakul S, Chattipakorn N, Watcharasaksilp K, Lord SR. Effects of tai chi on cognition and fall risk in older adults with mild cognitive impairment: a randomized controlled trial. *J Am Geriatr Soc.* 2017;65(4):721–7. <https://doi.org/10.1111/jgs.14594>.
105. Suttanon P, Hill KD, Said CM, Williams SB, Byrne KN, LoGiudice D, Lautenschlager NT, Dodd KJ. Feasibility, safety and preliminary evidence of the effectiveness of a home-based

- exercise programme for older people with Alzheimer's disease: a pilot randomized controlled trial. *Clin Rehabil.* 2013;27(5):427–38. <https://doi.org/10.1177/0269215512460877>.
106. Taylor ME, Lord SR, Brodaty H, Kurrle SE, Hamilton S, Ramsay E, Webster L, Payne NL, Close JC. A home-based, carer-enhanced exercise program improves balance and falls efficacy in community-dwelling older people with dementia. *Int Psychogeriatr.* 2017;29(1):81–91. <https://doi.org/10.1017/S1041610216001629>.
  107. Wesson J, Clemson L, Brodaty H, Lord S, Taylor M, Gitlin L, Close J. A feasibility study and pilot randomised trial of a tailored prevention program to reduce falls in older people with mild dementia. *BMC Geriatr.* 2013;13:89. <https://doi.org/10.1186/1471-2318-13-89>.
  108. Yoon JE, Lee SM, Lim HS, Kim TH, Jeon JK, Mun MH. The effects of cognitive activity combined with active extremity exercise on balance, walking activity, memory level and quality of life of an older adult sample with dementia. *J Phys Ther Sci.* 2013;25(12):1601–4. <https://doi.org/10.1589/jpts.25.1601>.
  109. Gietzelt M, Feldwieser F, Govercin M, Steinhagen-Thiessen E, Marschollek M. A prospective field study for sensor-based identification of fall risk in older people with dementia. *Inform Health Soc Care.* 2014;39(3–4):249–61. <https://doi.org/10.3109/17538157.2014.931851>.
  110. Spears GV, Roth CP, Miake-Lye IM, Saliba D, Shekelle PG, Ganz DA. Redesign of an electronic clinical reminder to prevent falls in older adults. *Med Care.* 2013;51(3 Suppl 1):S37–43. <https://doi.org/10.1097/MLR.0b013e31827807f8>.
  111. Juang LH, Wu MN. Fall down detection under smart home system. *J Med Syst.* 2015;39(10):107. <https://doi.org/10.1007/s10916-015-0286-3>.
  112. Pietrzak E, Cotea C, Pullman S. Does smart home technology prevent falls in community-dwelling older adults: a literature review. *Inform Prim Care.* 2014;21(3):105–12. <https://doi.org/10.14236/jhi.v21i3.64>.



# Delirium, Restraint Use and Falls

# 13

Pieter Heeren, Elke Detroyer, and Koen Milisen

---

## Background

Clinical decision-making based on the best available evidence is essential in preventing falls, especially among patients with pre-existing cognitive impairments who are at high risk of having delirium and/or being restrained. With the knowledge base of these conditions expanding, it is necessary that caregivers incorporate recent insights in clinical decision-making. This will not only have the potential to improve patient care and outcomes, it will also support caregivers in dealing with the choices they are confronted with.

This book chapter can help avoiding falls by (i) giving clinicians better understanding of the concept and epidemiology of delirium and restraint use, (ii) summarizing the consequences and risks of both conditions and (iii) providing insights into state-of-the-art management. In addition, links to supplementary materials will be provided.

---

P. Heeren

Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, Leuven, Belgium

Department of Geriatric Medicine, University Hospitals Leuven, Leuven, Belgium

Research Foundation Flanders, Brussels, Belgium

e-mail: [pieter.heeren@kuleuven.be](mailto:pieter.heeren@kuleuven.be)

E. Detroyer · K. Milisen (✉)

Department of Public Health and Primary Care, Academic Centre for Nursing and Midwifery, Leuven, Belgium

Department of Geriatric Medicine, University Hospitals Leuven, Leuven, Belgium

e-mail: [elke.detroyer@kuleuven.be](mailto:elke.detroyer@kuleuven.be); [koen.milisen@kuleuven.be](mailto:koen.milisen@kuleuven.be)

## **Delirium and Its Association with Falls**

### **Definition and Epidemiology of Delirium**

Delirium is a syndrome characterized by an acute and/or fluctuating disturbance of attention and awareness together with a disturbance in cognition or perception [1]. It can occur as a hypoactive (e.g. psychomotor retardation) or hyperactive (e.g. increased psychomotor activity) variant, and fluctuations between these two may be present [1, 2]. Delirium is a common problem in hospitals and nursing homes. In hospitals, the syndrome affects 11% to 68% of surgical (i.e. cardiac and orthopaedic surgery), 29% to 64% of medical and up to 88% of intensive care and palliative care unit patients [2–6]. In nursing homes, prevalence rates vary between 1.4% and 70.3%, depending on the diagnostic criteria used and the population being studied (i.e. aged 65+ years vs. 85+ years, prevalence of dementia) [7–9]. The prevalence of delirium in home care is much lower, ranging between 1% and 2% (i.e. population 65+ years) and 10% (i.e. population 85+ years) [7, 10]. Yet, it increases up to 22% in older persons with dementia [7].

### **Consequences of Delirium**

Patients with delirium are at increased risk for developing poor short- and long-term complications such as physical dysfunction, persistent cognitive decline and mortality across all settings (i.e. hospital, nursing home, home care), which consistently leads to additional healthcare costs [2, 9, 11–16]. Particularly in hospitalized patients (i.e. (geriatric) medicine, ICU, surgery and emergency wards) and nursing home residents, the syndrome is associated with a 1.5- to fourfold increase in the risk of mortality during the first 6 to 12 months follow-up [2, 9, 11–15], and a 12-fold increase in the risk for dementia up to 4 years [12]. Furthermore, hospitalized patients who develop delirium have a 2 to 7 days longer length of stay and a 2.5-fold increased risk for institutionalization up to 14 months compared to those without delirium [12, 16–18]. Additionally, delirium has been identified as a key contributor of inpatient falls [19–21]. Indeed, recent studies in the hospital setting reported high rates of fallers presenting symptoms of delirium (73–96%) [19–21]. Particularly in geriatric hospital populations, delirium is associated with a three- to sevenfold increase in the risk for falling [21].

---

### **Management of Delirium**

The association between delirium and falls has led to new insights in preventing and reducing falls. Indeed, evidence in hospital and nursing home settings supports the effectiveness of delirium management strategies not only on delirium but also on fall incidence [22–24]. Therefore, those strategies should be included in strategies to prevent falls.

The management of delirium is complex, and most studies are performed in hospital settings. In general, delirium management comprises (1) prevention by targeting risk factors of delirium, (2) detection of early signs of delirium and (3) treatment of delirium.

For the prevention of delirium, a variety of interventions have been developed including unicomponent (e.g. the use of earplugs, [25] staff education [26]) and multicomponent strategies (e.g. combination of staff education, redesign of the care system and introduction of standard protocols for the management of predisposing and precipitating factors of delirium [27]) (Table 13.1).

Within the multicomponent interventions [22, 23, 27, 31–33], the number of included components may vary between two [32] and thirteen [33]. Yet, it generally includes interventions regarding (1) staff education, (2) individualized care, (3) reorientation and (4) early mobilization.

To date, the multicomponent non-pharmacological intervention strategies have been recommended because of their preventive effects on delirium and falls in 30% to 50% and 60% to 64% of cases within medical and surgical older hospitalized persons, respectively [22, 23]. Table 13.2 gives an overview of non-pharmacological interventions to prevent delirium.

It is not yet known whether these interventions are also effective in a nursing home or home care population. A systematic review, summarizing studies in the institutional long-term care, [34] identified only two intervention studies in this setting. For example, a software-based intervention to identify risk of delirium related with medication was found to be effective on delirium incidence with moderate quality evidence, but not on secondary outcomes such as falls [34]. Yet, preliminary data about preventive delirium interventions in nursing homes exists [35, 36]. One study describes the development and pilot testing of such an intervention adapted from the Hospital Elder Life Program (HELP-LTC). [35] However, no control group was used to evaluate the effect of the program on delirium or falls. Further, one feasibility study evaluating a delirium prevention study found preliminary evidence suggesting a reduction in the rate of falls within nursing home residents [36].

**Table 13.1** Examples of predisposing (risk factors) and precipitating (causes) factors in the development of delirium [2, 28–30]

Predisposing factors	Precipitating factors
~ patients' vulnerability to develop delirium	~ insults/causes
Age	Infection
Premorbid cognitive problems (e.g. dementia)	Surgery
Physical frailty – low mobility	Medication
Severe illness	Pain
Visual impairment	Dehydration
Hearing impairment	Constipation
Polypharmacy	Urine retention
Malnutrition/dehydration	Renal failure
Renal impairment	Hypoxia
Previous delirium episode	Immobility/low mobility

**Table 13.2** Examples of non-pharmacological interventions to prevent delirium [2, 28–30]

<i>Prevent/address acute medical issues</i>	
Immobility/falls	Avoid the use of physical restraints Mobilize the patient at least three times a day (with assistance), keep walking aids nearby Encourage self-care Use physical and occupational therapy
Sleep disturbance	Maintain daytime wakefulness/encourage exposure to bright light during the day Avoid unnecessary awakenings during the night Implement non-pharmacological sleep-protocol, avoid sedatives, reduce light and noise at night
Infection	Identify and treat infection Avoid unnecessary catheterization/interventions Implement procedures regarding infection control
Pain	Assess and monitor for pain Start pain management
Urinary incontinence	Implement a toileting program (scheduled)
Feeding disorder	Monitor feeding intake If needed, provide feeding assistance and/or advice from dietician Provide supplementation as necessary
Pressure ulcers	Mobilize a patient; reposition if the patient is immobile Monitor pressure points
Vision and hearing problems	Ensure vision and hearing aids are available, working, and used by patients who need them
Hypoxia	Monitor oxygen saturation and ensure the saturation is above 95%
<i>Normalize function</i>	
Reorientation strategies	Encourage family involvement Reorient patients in time, place and person Provide calendars, clocks, signs Encourage family to bring in objects from home
Hospital environment	Reduce (background) noise Provide adequate lightning Approach patients calmly Listen to the patient
Education and participation of family	Provide education about delirium, how to interact with the patient and their role in restoring function Encourage patients to share their experience with healthcare staff

For the use of pharmacological interventions to prevent delirium, no clear evidence exists. A recent systematic review and meta-analysis included seven studies that compared antipsychotics with placebo or no treatment for delirium prevention after surgery [37]. No significant effect of the use of antipsychotics on delirium incidence was found (OR = 56, 95% confidence interval (CI) = 0.23–1.34) [37].

Not all delirium cases are preventable through preventive strategies. Indeed, daily observations for detection of early signs of delirium in patients at high risk (e.g. populations with advanced age, pre-existing cognitive impairment, severe illness) are necessary for the proper diagnosis and early treatment of delirium [38]. However, delirium remains frequently unrecognized or misdiagnosed (33–72%) in



routine care in hospitals [39–43], partially attributed to the failure of the healthcare team to systematically identify and tackle risk factors, and failure to use screening tools for early detection of delirium [42, 44]. In order to improve recognition of delirium, several delirium screening tools (e.g. Delirium Observation Screening Scale [45, 46], Intensive Care Delirium Screening Checklist [47]), tests for attention (e.g. digit span [48]) and cognitive assessment (e.g. Attention Screening Examination from the Confusion Assessment Method for the Intensive Care Unit [49]) and diagnostic tools (Confusion Assessment Method (CAM) [50], 4AT [51]) were developed. Yet, delirium can still be misdiagnosed because of its overlapping symptoms with dementia and depression.

Limited evidence supports the effectiveness of delirium treatment strategies. Therefore, recommendations regarding the treatment of delirium come from expert consensus. Well-established consensus guidelines include (1) identification and treatment of common modifiable causes (e.g. drugs, electrolyte disturbances, dehydration, infections, urinary and faecal disorders, myocardial and pulmonary disorders), (2) provision of a reassuring environment including an effective communication and reorientation and (3) use of medication for the management of symptoms of severe agitation and/or severe distress in patients with diagnosed delirium [38]. Table 13.3 gives an overview of the therapeutic strategy of patients with severely agitated delirium [28–30].

### Supplementary Information About Delirium

Nursing Standard of Practice Protocol: Delirium

<https://consultgeri.org/geriatric-topics/delirium>

**Table 13.3** Pharmacological treatment of patients with severely agitated delirium [28–30]

*Start with a low dose of one of the following medications, review every 24 hours (start low, go slow method), and maintain effective dose for about 2 to 3 days before tapering*

Medication	Doses/routes	Adverse effects
Haloperidol	Start with 0.25–0.5 mg orally, intramuscular or intravenous, may be repeated every 30 minutes Maximum 3 to 5 mg/24 hours	If 24-hour dose exceeds 3 mg: risk of EPS increases; use of intravenous haloperidol in monitored settings only
Quetiapine	Start with 12.5–25 mg orally Maximum 50 to 100 mg/24 hours	More sedating than haloperidol; risk of hypotension
Risperidone	Start with 0.5–1 mg orally or intramuscular Maximum 3 to 4 mg/24 hours	Less risk of EPS than with haloperidol, risk of hypotension
Olanzapine	Start with 2.5–5 mg orally, sublingual or intramuscular Maximum 10 to 20 mg/24 hours	More sedating than haloperidol
<b>If antipsychotics are contraindicated (in case of parkinsonism or Lewy body dementia), or in case of sedative and alcohol withdrawal; start benzodiazepines:</b>		
Lorazepam	Start with 0.5–1 mg orally, intramuscular or intravenous Maximum 2 to 4 mg/24 hours	More paradoxical excitation and respiratory depression than with haloperidol

EPS: extrapyramidal symptoms

4AT test

<https://www.the4at.com>

Delirium Observation Screening Scale

[https://www.researchgate.net/publication/10755447\\_The\\_Delirium\\_Observation\\_Screening\\_Scale](https://www.researchgate.net/publication/10755447_The_Delirium_Observation_Screening_Scale)

Monitoring delirium in the ICU /Confusion Assessment Method for the ICU/ Intensive Care Delirium Screening Checklist

<http://www.icudelirium.org/delirium/monitoring.html>

Hospital Elder Life Program/Confusion Assessment Method

<https://www.hospitalelderlifeprogram.org/>

---

## Restraint Use and Its Association with Falls

### Definition and Epidemiology of Restraint Use

Older adults are often restrained. Prevalence of restraint use varies between 3.5% and 11.8% in acute hospitals [52–54] and between 26.3% and 56% in nursing homes [52, 55, 56]. In contrast to in-hospital and residential care, its use and prevalence in home care has only recently become subject of research. The first studies in this setting report a prevalence variation between 5% and 24.7% [57–59]. These variations are not only setting specific but depend on several aspects such as methodology used, the population being studied and the selected definition [57].

A frequently used definition of physical restraints is Retsas' definition:

any device, material or equipment attached to or near a person's body and which cannot be controlled or easily removed by the person and which deliberately prevents or is deliberately intended to prevent a person's free body movement to a position of choice and/or a person's normal access to their body. [60]

Obvious examples of physical restraints include using bedrails, (limb/trunk) belts, nursing blanket and fixed tablet on a chair [61–63]. Less recognizable examples are removal of walking aids (e.g. walker), locking brakes on a wheelchair, locking a door, separation in a room, putting the bed against a wall and use of a geriatric chair [62, 63]. In addition, some classes of medication (e.g. sedatives, hypnotics, antidepressants, benzodiazepines) are considered restraints as well due to their restricting effect on self-determination [55, 63]. These examples of less recognizable and "chemical" restraints accentuate the need for broadening the definition of Retsas [60], which mainly focusses on physical restraints. Therefore, Scheepmans and colleagues extended Retsas' definition based on qualitative research findings into.

any actions performed by healthcare workers and/or relatives that restrict the patient's freedom to some extent (e.g. adaptation of the house, forced or camouflaged administration of medication). [57, 64]

The majority of studies within restraint use have been focusing on physical restraints only. To compare its prevalence better across future studies, an international, multidisciplinary expert panel reached consensus on an accepted research definition for physical restraints:

any action or procedure that prevents a person’s free body movement to a position of choice and/or normal access to his/her body by the use of any method, attached or adjacent to a person’s body that he/she cannot control or remove easily. [65]

Reasons and Consequences of Restraint Use

Regardless of the setting (i.e. acute hospitals, nursing homes, home care), restraints are primarily used as safety measures to prevent potential adverse events, such as fall incidents (e.g. fall out of bed) and accidental removal of medical devices (e.g. breathing tube, feeding/intravenous catheter) [66, 67]. Other reasons to restraint are controlling disturbing behaviour (e.g. removing dressing or clothes) or protecting the environment or other individuals (e.g. agitation, aggressive behaviour) [57, 67]. Although the decision-making process of restraint use is considered a complex collaboration between healthcare workers [67], sometimes these measures are performed at the request of the patient or an informal caregiver. Especially in home care, informal caregivers have more control on the use of these measures [57].

Numerous studies, mostly in long-term care facilities, examined what characteristics are associated with physical restraint use [67]. Among resident characteristics, low cognition (irrespective of the cause; e.g. delirium, dementia), serious mobility impairments and low activities of daily living have shown to be important risk factors [64, 67]. Other important risk factors are perceived risk of falling by nurses’ clinical judgement, behavioural problems and the informal caregiver’s well-being and satisfaction with care [64]. Associations between staffing characteristics and restraint use have been studied as well. However, findings on the importance of staff intensity and/or staff mix are inconsistent, as with other contextual factors [68]. This indicates that restraint use depends less on contextual and more on patient-related characteristics [68].

**Table 13.4** Negative consequences of physical restraints among restrained individuals [57, 67, 69]

Possible Primary and Secondary Consequences for Restrained Individuals	
Medical	Death (examples of possible causes are asphyxia, aspiration, blunt trauma to the chest, catecholamine rush), thrombosis, acute ischemia, contractures, pressure ulcers
Functional	Overall lower ADL performance; higher walking dependence, loss of mobility, balance problems, falls, urinary and faecal incontinence
Cognitive	Lower cognitive performance, delirium, loss of initiative
Emotional/ Social	Behavioural problems (e.g. shouting, agitation), negative feelings (e.g. frustration, fear, loneliness, mistrust with regard to nurses, loss of human dignity), social isolation

Despite its purpose of preventing adverse events, physical restraints can lead to serious consequences, including death [67, 69]. Table 13.4 gives a non-exhaustive overview of possible negative consequences that might occur due to restraint use. Although the prevalence of these consequences is not clear, caregivers should be aware of the risks related to these measures. A contradictory fact is that increased risk for falls or onset of delirium can both be a cause and a consequence of physical restraint use [66, 67], indicating the risk for a vicious cycle and the need for careful decision-making.

In addition to the consequences for restrained individuals, restraint use has an impact on other persons as well [70]. For example, relatives frequently report that ideas of denial, anger and worry are attributable to the restraint use among their beloved one [70, 71]. Healthcare workers describe experiencing inner conflicts, moral distress and mixed emotions as a result of applying physical restraints [62, 70]. These findings indicate that the consequences of restraint use are widespread and difficult to oversee.

---

## Restraint Reduction

Since every patient and context are unique, it is pivotal that the decision to restrain is based on individualized assessment. [70] This includes an openly discussed reflection of its benefits and disadvantages with all parties (i.e. the involved individual, relatives and the caregiving team). Ideally, this reflection is supported by an endorsed (organizational) policy that incorporates evidence- and ethics-based recommendations [70, 72]. Moreover, ethical aspects need to be addressed explicitly in this policy so these can support caregivers and relatives in dealing with dilemmas that originate from values such as dignity, autonomy, well-being and self-reliance [70, 72].

Although fall prevention is a frequently reported reason to restrain in clinical practice, there is no evidence supporting the effectiveness of restraints in decreasing fall incidence or fall-related injuries [66]. On contrary, restraints can increase the risk of falling and fall-related injuries [66]. Therefore, these measures should not be used as (part of) a strategy to prevent falls. This implies that the routinely use of bed rails is dissuaded. However, there are scenarios in which the use of bed rails is appropriate. To support clinicians in this decision-making, the National Patient Safety Agency formulated a risk matrix tool based on two patient characteristics: mental status and mobility (see Table 13.5) [73, 74].

Due to the negative consequences, ethical issues, legal grounds and lack of proven effectiveness, care standards challenge healthcare workers to reduce and even avoid restraint use [66, 70]. Several studies have shown that it is possible to reduce restraints (e.g. bedrails, belts) without increasing fall rates [61, 75–77]. However, this does not mean that all restraints can be avoided. None of these intervention studies could implement a 100% restraint-free policy, indicating that in some cases restraints are unavoidable. However, they should only be used when no alternatives are available (e.g. as a last resort option). Furthermore, patient

**Table 13.5** Risk matrix tool for appropriate bedrail use [73]

	Patient bed transfer mobility		
	Very immobile –bedfast or hoist dependent	Neither independent nor immobile	Can transfer without help from staff
Patient mental state			
Normal	Recommend bedrails	Recommend bedrails	Bedrails <i>not</i> recommended
Reduced alertness	Recommend bedrails	Use bedrails with care	Bedrails <i>not</i> recommended
Confused and alert	Use bedrails with care	Bedrails <i>not</i> recommended	Bedrails <i>not</i> recommended
Agitated	Bedrails <i>not</i> recommended	Bedrails <i>not</i> recommended	Bedrails <i>not</i> recommended

supervision should be increased during restraint use, meanwhile assuring care comfort for the patient (e.g. drinks and nurse alarm system within reach of patient, cave pinched wrists and ankles). Finally, the duration of restraining should be kept as short as possible, indicating regularly re-evaluating the patients' overall condition and behaviour [78].

Interventions for preventing and reducing the use of physical restraints are complex and their effect depends on several components. Old-generation intervention programs comprised primarily educational approaches targeting nursing staff [61, 79]. Their hypothesis was that restraint reduction is achievable via improving knowledge, attitudes and beliefs of nursing staff, and in turn can lead to a 'culture change' [61, 80]. However, despite several studies with prosperous results, a systematic review could not report proven effectiveness of this approach [61]. Moreover, it remained unclear which components should be part of the educational programs and its effect was judged overestimated. Thus, although the need for educating nurses as part of restraint reduction cannot be denied, additional components are deemed necessary in new-generation programs for more effective results. Although it is too early for evaluating these new-generation programs with systematic reviews and meta-analysis, there already are some inspiring examples, such as the guideline- and theory-based multicomponent intervention [80] and the EXBELT program [75–77].

The guideline- and theory-based multicomponent intervention led to reduction of physical restraint use in German nursing homes [80]. Percentage of physically restrained residents changed from 30.6% and 31.5% at baseline to 29.1% and 22.6% at 6-month follow-up in the control and intervention group, respectively. The 6.5% difference (95% confidence interval (CI) = 0.6%–12.4%) between groups at 6-month follow-up in favour of the intervention corresponded with a cluster-adjusted odds ratio of 0.71 (95% CI = 0.52–0.97;  $p = 0.03$ ). In addition, the intervention group did not differ significantly regarding falls, fall-related fractures and psychotropic medication prescriptions. This intervention was developed using the UK Medical Research Council's methodological guidance for the development and evaluation of complex interventions [81]. Examples of the intervention components were (i) group sessions for all nursing staff (focussing on key aspects such as restraint

definition, consequences, legal aspects, guideline recommendations and subjective attitudes and experiences); (ii) additional training for nominated key nurses/clinical role models (including advanced education for in-depth guideline knowledge and individual discussions on restraint prevalence and nurses' knowledge) and (iii) supportive materials (such as short versions of the guideline and flyers) for nurses, residents, relatives and legal guardians. For more details, we refer to the publication and the supplementary online content of this cluster randomized controlled trial.

EXBELT is another example of a multicomponent intervention program that led to a decrease of restraint use (i.e. belts, full-enclosure bedrails and sleep suits) without increasing the use of other physical restraints, psychoactive drugs, or falls and fall-related injuries [75–77]. The original EXBELT study in Dutch psychogeriatric nursing home wards provided 8-month follow-up and reported a 50% decrease in belt use (odds ratio (OR) = 0.48, 95% CI = 0.28–0.81;  $p = 0.005$ ) [75]. Key components of this intervention were institutional policy change, nursing home staff education, consultation by a nurse specialist and availability of alternative interventions (such as balance training, exercise, special pillows and lower beds). However, besides restraint reduction, the most outstanding effect of the EXBELT program was restraint prevention. Two follow-up quasi-experimental studies documented this [76, 77]. Although the samples of the first study on short-term prevention effect among newly admitted residents after EXBELT implementation were rather small, there were substantial restraint use differences between control group patients ( $n = 20$ ; restraint use in 15% and 20% of residents at 4 and 8 months, respectively) and intervention group patients ( $n = 29$ ; restraint use in 3% and 0% of residents at 4 and 8 months, respectively) (OR = 0.08; 95% CI = 0.01–0.76;  $p = 0.03$ ) [76]. This restraint reduction was again obtained without increasing the use of other physical restraints, psychoactive drugs, or falls and fall-related injuries. The second study scrutinized the EXBELT effect on both a panel group (i.e. residents present at baseline and 24 months after baseline;  $n = 225$ ) and a survey group (i.e. residents present at 24 months after baseline;  $n = 689$ ) [77]. Main findings were an important decrease in belt use among panel group residents (OR = 0.35; 95% CI = 0.13–0.93;  $p = 0.04$ ) and a substantial difference in belt use between control and intervention patients among the survey group (belt use was 13% and 3% in control and intervention patients at 24 months after baseline, respectively;  $p < 0.001$ ) [77]. In addition, the use of other restrictive restraints at 24 months decreased as well. Therefore, the EXBELT program can be considered suitable for minimizing (belt) restraint use on both short and long term.

### **Supplementary Information About Restraint Use**

Nursing Standard of Practice Protocol: Physical Restraints and Side Rails in Acute and Critical Care Settings

<https://consultgeri.org/geriatric-topics/physical-restraints>

How to prevent restraint deaths

[https://www.jointcommission.org/assets/1/18/SEA\\_8.pdf](https://www.jointcommission.org/assets/1/18/SEA_8.pdf)

Resources for reviewing or developing a bedrail policy

<http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=60110&type=full&servicetype=Attachment>

## Conclusion

Patients with delirium or restraints are at increased risk for serious adverse events, including falls and fall-related injuries. Although state-of-the-art evidence supports non-pharmacological management as the best way for prevention, delirium or restraint use are not always avoidable. Severity and duration of these conditions can then be minimized with individualized assessment followed by multicomponent interventions, regular re-evaluation and follow-up in order to lower the risk of falls and fall-related injuries.

## References

1. American Psychiatric Association. Neurocognitive disorders. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 2013. p. 591–643.
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* (London, England). 2014;383(9920):911–22. [https://doi.org/10.1016/s0140-6736\(13\)60688-1](https://doi.org/10.1016/s0140-6736(13)60688-1).
3. Lindsay JRK, Rolfson D. The epidemiology of delirium. In: Lindsay JRK, Macdonald A, editors. *Delirium in old age*. New York: Oxford University Press; 2002. p. 27–50.
4. Detroyer E, Dobbels F, Verfaillie E, Meyfroidt G, Sergeant P, Milisen K. Is preoperative anxiety and depression associated with onset of delirium after cardiac surgery in older patients? A prospective cohort study. *J Am Geriatr Soc*. 2008;56(12):2278–84.
5. Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med*. 2000;160(6):786–94.
6. Mehta S, Cook D, Devlin JW, Skrobik Y, Meade M, Fergusson D, et al. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med*. 2015;43(3):557–66. <https://doi.org/10.1097/ccm.0000000000000727>.
7. de Lange E, Verhaak PF, van der Meer K. Prevalence, presentation and prognosis of delirium in older people in the population, at home and in long term care: a review. *Int J Geriatr Psychiatry*. 2013;28(2):127–34. <https://doi.org/10.1002/gps.3814>.
8. Boorsma M, Joling KJ, Frijters DH, Ribbe ME, Nijpels G, van Hout HP. The prevalence, incidence and risk factors for delirium in Dutch nursing homes and residential care homes. *Int J Geriatr Psychiatry*. 2012;27(7):709–15. <https://doi.org/10.1002/gps.2770>.
9. Siddiqi N, Clegg A, Young J. Delirium in care homes. *Rev Clin Gerontol*. 2009;19(4):309–16.
10. Bohlken J, Kostev K. Prevalence and risk factors for delirium diagnosis in patients followed in general practices in Germany. *Int Psychogeriatr*. 2018;30(4):511–8. <https://doi.org/10.1017/s1041610217002587>.
11. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Arch Intern Med*. 2002;162(4):457–63.
12. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443–51. <https://doi.org/10.1001/jama.2010.1013>.
13. Olin K, Eriksdotter-Jonhagen M, Jansson A, Herrington MK, Kristiansson M, Permert J. Postoperative delirium in elderly patients after major abdominal surgery. *Br J Surg*. 2005;92(12):1559–64. <https://doi.org/10.1002/bjs.5053>.



14. Ganai S, Lee KF, Merrill A, Lee MH, Bellantonio S, Brennan M, et al. Adverse outcomes of geriatric patients undergoing abdominal surgery who are at high risk for delirium. *Archives Surg* (Chicago, Ill: 1960). 2007;142(11):1072–8. <https://doi.org/10.1001/archsurg.142.11.1072>.
15. Siddiqi N, House A, Holmes J. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing*. 2006;35:350–64.
16. Crocker E, Beggs T, Hassan A, Denault A, Lamarche Y, Bagshaw S, et al. Long-term effects of postoperative delirium in patients undergoing cardiac operation: a systematic review. *Ann Thorac Surg*. 2016;102(4):1391–9. <https://doi.org/10.1016/j.athoracsur.2016.04.071>.
17. Aitken SJ, Blyth FM, Naganathan V. Incidence, prognostic factors and impact of postoperative delirium after major vascular surgery: a meta-analysis and systematic review. *Vascular Medicine* (London, England). 2017;22(5):387–97. <https://doi.org/10.1177/1358863x17721639>.
18. O'Keeffe S, Lavan J. The prognostic significance of delirium in older hospital patients. *J Am Geriatr Soc*. 1997;45(2):174–8.
19. Babine RL, Hyrkas KE, Bachand DA, Chapman JL, Fuller VJ, Honess CA, et al. Falls in a tertiary care hospital-association with delirium: a replication study. *Psychosomatics*. 2016;57(3):273–82. <https://doi.org/10.1016/j.psych.2016.01.003>.
20. Lakatos BE, Capasso V, Mitchell MT, Kilroy SM, Lussier-Cushing M, Sumner L, et al. Falls in the general hospital: association with delirium, advanced age, and specific surgical procedures. *Psychosomatics*. 2009;50(3):218–26. <https://doi.org/10.1176/appi.psy.50.3.218>.
21. Mazur K, Wilczynski K, Szewieczek J. Geriatric falls in the context of a hospital fall prevention program: delirium, low body mass index, and other risk factors. *Clin Interv Aging*. 2016;11:1253–61. <https://doi.org/10.2147/cia.S115755>.
22. Hshieh TT, Yue J, Oh E, Puelle M, Dowal S, Trivison T, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med*. 2015;175(4):512–20. <https://doi.org/10.1001/jamainternmed.2014.7779>.
23. Martinez F, Tobar C, Hill N. Preventing delirium: should non-pharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature. *Age Ageing*. 2015;44(2):196–204. <https://doi.org/10.1093/ageing/afu173>.
24. Babine RL, Hyrkas KE, Hallen S, Wierman HR, Bachand DA, Chapman JL, et al. Falls and delirium in an acute care setting: a retrospective chart review before and after an organisation-wide interprofessional education. *J Clin Nurs*. 2018;27(7–8):e1429–e41. <https://doi.org/10.1111/jocn.14259>.
25. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. *Critical Care* (London, England). 2012;16(3):R73. <https://doi.org/10.1186/cc11330>.
26. Rockwood K. Educational interventions in delirium. *Dement Geriatr Cogn Disord*. 1999;10(5):426–9. <https://doi.org/10.1159/000017183>.
27. Milisen K, Lemiengre J, Braes T, Foreman MD. Multicomponent intervention strategies for managing delirium in hospitalized older people: systematic review. *J Adv Nurs*. 2005;52(1):79–90. <https://doi.org/10.1111/j.1365-2648.2005.03557.x>.
28. Healthcare Improvement Scotland. Think delirium. Improving the care for older people: Delirium toolkit. 2014.
29. Marcantonio ER. Delirium in Hospitalized Older Adults. *N Engl J Med*. 2017;377(15):1456–66. <https://doi.org/10.1056/NEJMc1605501>.
30. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: advances in diagnosis and treatment. *JAMA*. 2017;318(12):1161–74. <https://doi.org/10.1001/jama.2017.12067>.
31. Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *The Cochrane Database Systematic Reviews*. 2016;3:Cd005563. <https://doi.org/10.1002/14651858.CD005563.pub3>.
32. Jeffs KJ, Berlowitz DJ, Grant S, Lawlor V, Graco M, de Morton NA, et al. An enhanced exercise and cognitive programme does not appear to reduce incident delirium in hospitalised patients: a randomised controlled trial. *BMJ Open*. 2013;3(6) <https://doi.org/10.1136/bmjopen-2013-002569>.

33. Hempenius L, Slaets JP, van Asselt D, de Bock GH, Wiggers T, van Leeuwen BL. Outcomes of a geriatric liaison intervention to prevent the development of postoperative delirium in frail elderly Cancer patients: report on a multicentre, randomized. Controlled Trial PloS One. 2013;8(6):e64834. <https://doi.org/10.1371/journal.pone.0064834>.
34. Gonzalez-Gil T. Interventions for preventing delirium in older people in institutional long-term care. Int J Nurs Stud. 2016;55:133–4. <https://doi.org/10.1016/j.ijnurstu.2015.12.009>.
35. Boockvar KS, Teresi JA, Inouye SK. Preliminary data: an adapted hospital elder life program to prevent delirium and reduce complications of acute illness in long-term care delivered by certified nursing assistants. J Am Geriatr Soc. 2016;64(5):1108–13. <https://doi.org/10.1111/jgs.14091>.
36. Siddiqi N, Cheater F, Collinson M, Farrin A, Forster A, George D, et al. The PiTSTOP study: a feasibility cluster randomized trial of delirium prevention in care homes for older people. Age Ageing. 2016;45(5):652–61. <https://doi.org/10.1093/ageing/afw091>.
37. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2016;64(4):705–14. <https://doi.org/10.1111/jgs.14076>.
38. National Institute for Health and Care Excellence. Delirium: prevention, diagnosis and management. 2015. <https://www.nice.org.uk/Guidance/CG103>. Accessed 14 July 2018.
39. Collins N, Blanchard MR, Tookman A, Sampson EL. Detection of delirium in the acute hospital. Age Ageing. 2010;39(1):131–5. <https://doi.org/10.1093/ageing/afp201>.
40. Elie M, Rousseau F, Cole M, Primeau F, McCusker J, Bellavance F. Prevalence and detection of delirium in elderly emergency department patients. CMAJ. 2000;163(8):977–81.
41. Lemiengre J, Nelis T, Joosten E, Braes T, Foreman M, Gastmans C, et al. Detection of delirium by bedside nurses using the confusion assessment method. J Am Geriatr Soc. 2006;54(4):685–9. <https://doi.org/10.1111/j.1532-5415.2006.00667.x>.
42. Milisen K, Foreman MD, Wouters B, Driesen R, Godderis J, Abraham IL, et al. Documentation of delirium in elderly patients with hip fracture. J Gerontol Nurs. 2002;28(11):23–9.
43. Steis MR, Fick DM. Are nurses recognizing delirium? A systematic review. J Gerontol Nurs. 2008;34(9):40–8.
44. Fick D, Foreman M. Consequences of not recognizing delirium superimposed on dementia in hospitalized elderly individuals. J Gerontol Nurs. 2000;26(1):30–40.
45. Schuurmans MJ, Shorridge-Baggett LM, Duursma SA. The delirium observation screening scale: a screening instrument for delirium. Res Theory Nurs Pract. 2003;17(1):31–50.
46. Detroyer E, Clement PM, Baeten N, Pennemans M, Decruyenaere M, Vandenbergh J, et al. Detection of delirium in palliative care unit patients: a prospective descriptive study of the delirium observation screening scale administered by bedside nurses. Palliat Med. 2014;28(1):79–86. <https://doi.org/10.1177/0269216313492187>.
47. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive care delirium screening checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27(5):859–64.
48. O'Keeffe ST, Gosney MA. Assessing attentiveness in older hospital patients: global assessment versus tests of attention. J Am Geriatr Soc. 1997;45(4):470–3.
49. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001;286(21):2703–10.
50. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941–8.
51. Bellelli G, Morandi A, Davis DH, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing. 2014;43(4):496–502. <https://doi.org/10.1093/ageing/afu021>.
52. Hofmann H, Schorro E, Haastert B, Meyer G. Use of physical restraints in nursing homes: a multicentre cross-sectional study. BMC Geriatr. 2015;15:129. <https://doi.org/10.1186/s12877-015-0125-x>.

53. Kruger C, Mayer H, Haastert B, Meyer G. Use of physical restraints in acute hospitals in Germany: a multi-Centre cross-sectional study. *Int J Nurs Stud*. 2013;50(12):1599–606. <https://doi.org/10.1016/j.ijnurstu.2013.05.005>.
54. Raguán B, Wolfowitz E, Gil E. Use of physical restraints in a general hospital: a cross-sectional observational study. *Isr Med Assoc J*. 2015;17(10):633–8.
55. Feng Z, Hirdes JP, Smith TF, Finne-Soveri H, Chi I, Du Pasquier JN, et al. Use of physical restraints and antipsychotic medications in nursing homes: a cross-national study. *Int J Geriatr Psychiatry*. 2009;24(10):1110–8. <https://doi.org/10.1002/gps.2232>.
56. Huizing AR, Hamers JP, de Jonge J, Candel M, Berger MP. Organisational determinants of the use of physical restraints: a multilevel approach. *Social Sci Med* (1982). 2007;65(5):924–33. <https://doi.org/10.1016/j.socscimed.2007.04.030>.
57. Scheepmans K, Dierckx de Casterle B, Paquay L, Van Gansbeke H, Milisen K. Restraint use in older adults receiving home care. *J Am Geriatr Soc*. 2017;65(8):1769–76. <https://doi.org/10.1111/jgs.14880>.
58. Beerens HC, Sutcliffe C, Renom-Guiteras A, Soto ME, Suhonen R, Zabalegui A, et al. Quality of life and quality of care for people with dementia receiving long term institutional care or professional home care: the European RightTimePlaceCare study. *J Am Med Dir Assoc*. 2014;15(1):54–61. <https://doi.org/10.1016/j.jamda.2013.09.010>.
59. Hamers JP, Bleijlevens MH, Gulpers MJ, Verbeek H. Behind closed doors: involuntary treatment in care of persons with cognitive impairment at home in the Netherlands. *J Am Geriatr Soc*. 2016;64(2):354–8. <https://doi.org/10.1111/jgs.13946>.
60. Retsas AP. Survey findings describing the use of physical restraints in nursing homes in Victoria, Australia. *Int J Nurs Stud*. 1998;35(3):184–91.
61. Mohler R, Richter T, Kopke S, Meyer G. Interventions for preventing and reducing the use of physical restraints in long-term geriatric care - a Cochrane review. *J Clin Nurs*. 2012;21(21–22):3070–81. <https://doi.org/10.1111/j.1365-2702.2012.04153.x>.
62. Scheepmans K, Dierckx de Casterle B, Paquay L, Van Gansbeke H, Boonen S, Milisen K. Restraint use in home care: a qualitative study from a nursing perspective. *BMC Geriatr*. 2014;14:17. <https://doi.org/10.1186/1471-2318-14-17>.
63. Scheepmans K, Dierckx de Casterle B, Paquay L, Milisen K. Restraint use in older adults in home care: a systematic review. *Inter J Nursing Studies*. 2018;79:122–36. <https://doi.org/10.1016/j.ijnurstu.2017.11.008>.
64. Scheepmans K, Milisen K, Vanbrabant K, Paquay L, Van Gansbeke H, Dierckx de Casterle B. Factors associated with use of restraints on older adults with home care: a cross sectional study. *Inter J Nursing Studies*. 2019;89:39–45. <https://doi.org/10.1016/j.ijnurstu.2018.07.019>.
65. Bleijlevens MH, Wagner LM, Capezuti E, Hamers JP. Physical restraints: consensus of a research definition using a modified Delphi technique. *J Am Geriatr Soc*. 2016;64(11):2307–10. <https://doi.org/10.1111/jgs.14435>.
66. Sze TW, Leng CY, Lin SK. The effectiveness of physical restraints in reducing falls among adults in acute care hospitals and nursing homes: a systematic review. *JBIS Library Systematic Rev*. 2012;10(5):307–51. <https://doi.org/10.11124/jbisr-2012-4>.
67. Hofmann H, Hahn S. Characteristics of nursing home residents and physical restraint: a systematic literature review. *J Clin Nurs*. 2014;23(21–22):3012–24. <https://doi.org/10.1111/jocn.12384>.
68. Heeren P, Van de Water G, De Paepe L, Boonen S, Vleugels A, Milisen K. Staffing levels and the use of physical restraints in nursing homes: a multicenter study. *J Gerontol Nurs*. 2014;40(12):48–54. <https://doi.org/10.3928/00989134-20140407-03>.
69. Mohr WK, Petti TA, Mohr BD. Adverse effects associated with physical restraint. *Can J Psychiatry*. 2003;48(5):330–7. <https://doi.org/10.1177/070674370304800509>.
70. Gastmans C, Milisen K. Use of physical restraint in nursing homes: clinical-ethical considerations. *J Med Ethics*. 2006;32(3):148–52. <https://doi.org/10.1136/jme.2005.012708>.
71. Saarnio R, Isola A. Use of physical restraint in institutional elderly care in Finland: perspectives of patients and their family members. *Res Gerontol Nurs*. 2009;2(4):276–86. <https://doi.org/10.3928/19404921-20090706-02>.

72. Scheepmans K. Restraint use in home care: a multimethod analysis. Leuven: Acco; 2018.
73. Flatharta TO, Haugh J, Robinson SM, O'Keeffe ST. Prevalence and predictors of bedrail use in an acute hospital. *Age Ageing*. 2014;43(6):801–5. <https://doi.org/10.1093/ageing/afu081>.
74. National Patient Safety Agency. Resources for reviewing or developing a bedrail policy. London; 2007.
75. Gulpers MJ, Bleijlevens MH, Ambergen T, Capezuti E, van Rossum E, Hamers JP. Belt restraint reduction in nursing homes: effects of a multicomponent intervention program. *J Am Geriatr Soc*. 2011;59(11):2029–36. <https://doi.org/10.1111/j.1532-5415.2011.03662.x>.
76. Gulpers MJ, Bleijlevens MH, Capezuti E, van Rossum E, Ambergen T, Hamers JP. Preventing belt restraint use in newly admitted residents in nursing homes: a quasi-experimental study. *Int J Nurs Stud*. 2012;49(12):1473–9. <https://doi.org/10.1016/j.ijnurstu.2012.07.013>.
77. Gulpers MJ, Bleijlevens MH, Ambergen T, Capezuti E, van Rossum E, Hamers JP. Reduction of belt restraint use: long-term effects of the EXBELT intervention. *J Am Geriatr Soc*. 2013;61(1):107–12. <https://doi.org/10.1111/jgs.12057>.
78. Milisen K, Vandenbergh J, Sabbe M, Lagae R, Braes T, Vanderlinden V, et al. Richtlijn betreffende vrijheidsbeperkende maatregelen ter beveiliging van de patiënt in de UZ Leuven. *Tijdschrift voor Geneeskunde*. 2006;62(23):1659–63.
79. Evans D, Wood J, Lambert L. A review of physical restraint minimization in the acute and residential care settings. *J Adv Nurs*. 2002;40(6):616–25.
80. Kopke S, Muhlhauser I, Gerlach A, Haut A, Haastert B, Mohler R, et al. Effect of a guideline-based multicomponent intervention on use of physical restraints in nursing homes: a randomized controlled trial. *JAMA*. 2012;307(20):2177–84. <https://doi.org/10.1001/jama.2012.4517>.
81. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud*. 2013;50(5):587–92. <https://doi.org/10.1016/j.ijnurstu.2012.09.010>.



# Approaches for Falls Prevention in Hospitals and Nursing Home Settings

# 14

Jesse Zanker and Gustavo Duque

## Introduction

This chapter will examine and present evidence-based interventions for falls prevention in nursing homes and hospitals, considering the unique risk factors of older people in these settings. Two measures are used to describe the effect an approach or intervention may have on falls: rate of falls and risk of falling. Rate of falls describes the number of falls per person per year, presented as rate ratio. Risk of falling describes the number of people who fell once or more in a year compared with those who did not fall, presented as risk ratio.

Falls in older people are a common problem and carry significant consequences for individuals and society. Falls can result in serious injury, hospitalization, death, anxiety and depression, and reduction in quality of life [1–3]. The risk of falls and falls-related complications is associated with age, and given the population is aging, the incidence of falls is expected to rise [4]. While falls can occur across all demographics, a number of population groups are at a significantly higher risk of falls and falls-related complications. Older people living in long-term care facilities, or nursing homes, and those who are hospitalized are at significantly higher risk than the general population [5]. The incidence of falls in nursing homes is three times greater than those in the community and this risk is even higher in geriatric and older-age psychiatry hospital wards [6, 7]. The individual, social, and economic burden of falls and falls-related complications in these population groups is high; thus, falls prevention programs are a major focus of governments and institutions worldwide.

---

J. Zanker · G. Duque (✉)

Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St. Albans, VIC, Australia

Department of Medicine-Western Health, Melbourne Medical School, The University of Melbourne, St. Albans, VIC, Australia

Department of Geriatric Medicine, Western Health, St. Albans, VIC, Australia  
e-mail: [gustavo.duque@unimelb.edu.au](mailto:gustavo.duque@unimelb.edu.au)

© Springer Nature Switzerland AG 2020

M. Montero-Odasso, R. Camicioli (eds.), *Falls and Cognition in Older Persons*,  
[https://doi.org/10.1007/978-3-030-24233-6\\_14](https://doi.org/10.1007/978-3-030-24233-6_14)

245

## Falls Risk Factors

To best address the approach to falls prevention in hospitals and nursing homes, an examination of the unique features of this demographic is required.

In nursing homes, falls are more common in men and approximately three quarters of falls occur in residents' own rooms and bathrooms [8]. The degree of support or assistance residents require with personal tasks, transfers, and ambulation also predict risk of falls [9]. Those requiring the least or the highest amount of care are at highest risk of falls in the nursing home population [8]. However, those who are unable to stand or transfer unaided are at lower risk than those independently standing or transferring [9]. The degree of risk of the individual and their specific circumstances must be considered when applying falls prevention principles and appropriate interventions.

The hospitalized, older population is at uniquely higher risk of falls than most other demographics. Acute illness, coupled with underlying vulnerabilities such as frailty or cognitive impairment and unfavorable hospital environment, creates a high-risk setting for older people. Key individual risk factors for falls in hospitalized older people include gait instability, delirium, dementia, incontinence, stroke, falls history, "culprit" medications, and need for transfer assistance [10, 11]. Certain features of the hospital environment also contribute to an increase risk of falls in the older population. A noisy environment resulting in disturbed sleep–wake cycle and carpeted floors are two features recognized as significantly increasing the risk of falls in older, hospitalized people [11].

---

## Falls in Nursing Homes

The global population is aging, and as such, the absolute and relative number of people living in nursing homes is increasing [12]. The reasons older people transition into nursing homes are highly variable and comprise individual and societal deficits across biological, psychological, cognitive, and social domains. Many of these deficits also contribute to individual frailty, which independently predicts risk of falls [13]. Approximately 40% of admissions to nursing homes for permanent living are the result of falls, and these residents are at heightened risk of falls within nursing homes [14]. Men living in nursing homes are almost twice as likely to fall than women in the same setting [8].

While falls in nursing homes are common, they are not inevitable. Vitamin D supplementation may reduce the rate of falls but not risk of falling [15]. A recent Cochrane Review demonstrated that interventions such as exercise, medication review, and multifactorial interventions may make little or no difference to the risk of falling in nursing home facilities [15]. Further, balancing falls prevention programs with safety culture and mobility restriction must be carefully considered [14]. The variability in level of care, institutional standards, and local management need to be considered when applying targeted, specific interventions for falls prevention.

## Evidence-Based Approaches to Falls Prevention in Nursing Homes

In 2018, Cameron et al. published a Cochrane Review that examined studies of falls prevention interventions in nursing homes and hospitals [15]. Another recent systematic review and meta-analysis did not differentiate between community and nursing home participants; thus, it is of limited value in this discussion [16]. Seventy-one studies across four continents were included in the Cochrane Review, and levels of care from intermediate, high, and mixed were represented. A cross-section of interventions was examined and included single, multiple, or multifactorial interventions [15]. The categories of interventions include exercise, medication review, vitamin D supplementation, multivitamin supplementation, technological interventions, staff training, and service model development. A summary of these findings and their effects are presented in Table 14.1.

### Exercise

Exercise programs were shown to have no effect on the rate of falls and risk of falling in older people when combining participants from all levels of care [15]. However, there was a significant reduction on rate of falls and a trend toward reduction of risk of falls in intermediate-level-care nursing homes when compared with high-level-care nursing homes. High-level-care nursing homes tend to care for residents with higher levels of disability, who may be less responsive to exercise interventions. Conversely, exercise interventions in a frail subgroup of nursing home residents actually increased the risk of falling [15]. A 2017 systematic review and meta-analysis on prevention of falls in all settings found that exercise alone reduces

**Table 14.1** Effect of interventions on falls in nursing homes

	Single	Multiple	Multifactorial
Exercise	Increased rate in HLC Decreased rate in ILC	No effect	
Medication review	No effect or increased rate		
Vitamin D supplementation	Decreased rate in vit D deficient people		
Social Staff training Service model – Dementia-care mapping	No effect Reduced rate (very low quality)		
Exercise, fluids, and toileting		No effect	
Sunlight exposure and calcium		No effect	
Tailored combination of interventions			Possibly reduced although inconclusive

*HLC* High-level care, *ILC* Intermediate-level care



**Table 14.2** The effect of different exercises on falls

Exercise	Rate of falls	Risk of falling
Balance training (separated treadmill [17] or balance with feedback [18])	Reduced	No effect
Balance training (standing on one leg [19])	Reduced	No effect
Functional balance training “Functional walking” [20]	Increased	No effect
Goal setting for ADLs [21]	No effect	No effect
Tai Chi [22, 23]	No effect	
Exercise combination (balance and fitness) [20, 23–28]	No effect	No effect

*ADLs* Activities of daily living

the risk of injurious falls but that there was no subgroup analysis of nursing home falls prevention [16].

There is variability of the types of exercise programs and the population to which it is applied. Table 14.2 summarizes the effect different exercise interventions have on rate of falls and risk of falling in nursing home residents. The pooled evidence suggests that the greatest value in reducing the rate of falls is in balance and functional balance training, particularly in nursing home residents requiring intermediate-level care; however, the quality of evidence is low [15].

## Medication Review

A medication review involves an assessment of an older person’s prescribed medications with the purpose of rationalizing the regimen. This may involve removing medications that are not providing benefit or that may cause harm. A medication review can be undertaken by a trained pharmacist or doctor.

The evidence base for the effect medication reviews have on falls is limited and of poor quality [15]. In nursing home residents, it has been studied in two scenarios. First, a medication review may be undertaken for those people transitioning from a hospital to a nursing home. A one-off pharmacist-led medication review during transition did not demonstrate an effect of risk of falling [29–31]. Second, a medication review may be undertaken for residents within the nursing home as a one-off or continuing process. Conflicting results have been shown in this setting with and ongoing pharmacist review showing an increased rate of falls, [32] and a one-off pharmacist review demonstrating a decreased rate of falls [31].

A recent systematic review and meta-analysis revealed that medication reviews in nursing homes have no effect on mortality or hospitalization, albeit more research is required [33]. Nevertheless, reviewing medications and rationalizing where appropriate is good medical practice; however, the evidence suggests that the process may not have a meaningful impact on falls in older people transitioning to or living in nursing homes.

## Vitamin and Mineral Supplementation

Vitamin D has a number of actions in the body including effects on muscle and bone metabolism, and central nervous system growth, protection, and neurotransmission [34–36]. Supplementation of vitamin D has been shown to improve muscle strength in adults [37]. In nursing home residents, vitamin D supplementation in vitamin D–deficient residents significantly reduces the rate of falls [15].

A number of trials have examined vitamin D supplementation in nursing homes. Supplementation of vitamin D (25(OH)D3 or 25(OH)D2) in vitamin D–deficient nursing home residents resulted in a significant reduction in the rate of falls, but no change in the risk of falling with moderate quality evidence [38–42]. The addition of calcium to vitamin D supplementation had no effect on the risk of falling [40]. A trial involving multivitamin supplementation (which included vitamin D) in nursing home residents demonstrated a significant reduction in rate of falls but not in risk of falling [43]. It is unclear whether the benefit gained from multivitamin supplementation was due to the effect of vitamin D, or the other components in the multivitamin, or both.

## Social Environment

A number of social or structural interventions to reduce falls within nursing homes have been studied. These interventions focus on staff, caregivers, and systems rather than on residents within the nursing home. Social environment interventions comprise two categories: staff training and service model change.

Two studies in which the intervention was education of staff, focusing on either falls prevention or patient safety, demonstrated no significant reduction in the rate of falls of nursing home residents [44].

Service model interventions, such as falls assessment tools and a practice nurse employed to implement best practice strategies, have failed to demonstrate a significant effect on rate of falls or risk of falling [45, 46]. However, dementia-care mapping, which is a method of implementing person-centered care based on the social and psychological theory of dementia, demonstrated a significant reduction in rate of falls [47]. However, the quality of evidence was assessed as very low and thus more research is required in this area [15].

## Psychological Interventions

Two studies have examined the effect of psychological interventions of falls. One study employed cognitive–behavioral therapy via computer-based training, [48] and another study employed an experienced facilitator to provide the therapy [49]. The quality of evidence and rate of falling was very low; therefore, uncertainty remains as to the effectiveness of psychological interventions on falls [15].

## Multiple Interventions

These comprise interventions in nursing homes in which the same combinations of interventions are provided to all participants. Intervention that involved exercises, fluids, scheduled toileting, and sunlight exposure, in addition to calcium supplementation, did not demonstrate a significant effect on rate of falls or risk of falling and the quality of evidence was very low [50, 51].

## Multifactorial Interventions

Multifactorial interventions are those in which multiple interventions are tailored and delivered based on the nursing home resident's risk profile. There have been nine trials examining the effects of multifactorial interventions, with mixed results [15]. Pooled data demonstrated a possible benefit of multifactorial, tailored interventions; however, this was an inconclusive result and the quality of evidence was very low [52–60]. No benefit was observed on examination of the effect of multifactorial interventions on residents with cognitive impairment [15].

---

## Falls in Hospitals

Falls in hospitals are common. As with falls in nursing homes, falls in hospitals should not be viewed as inevitable. Hospitals pose a great number of environmental and social hazards for older people, particularly when combined with individual factors such as acute illness, cognitive impairment, delirium, frailty, and functional dependence. Further, the acuity of hospitals and the short length of stay means that prevention strategies applicable to nursing homes may not apply in hospital settings [61].

The prevention of falls in hospitals is a focus of governments worldwide with some countries enforcing financial penalties on hospitals for not reaching falls prevention targets [62]. Growden et al. argue that the fear of falls in hospitals has led to a “culture of immobility.” [62] Hospital patients spend over 95% of their time in bed [63] and some argue that mobility restriction may increase risk of in-hospital and post-hospital falls [62].

Although a great number of studies have been undertaken on falls prevention strategies in hospitals, additional methodologically sound trials are required to establish more conclusive evidence. Further, the evidence that exists must be examined as to whether it is applicable to the target population and setting. The importance of individualizing interventions has been recognized by the National Institute of Clinical Excellence (NICE) in the United Kingdom. The quality statements on preventing falls in older people, which are implemented across the public health system in the United Kingdom, are summarized in Fig. 14.1 [64]. Through general recommendations, the NICE statement addresses falls in hospitalized patients.

- Practitioners should ask older people about falls during routine assessments and hospital admissions
- Multifactorial falls assessments are offered to older adults at risk of falling
- Multifactorial fall interventions are provided to those at risk of falling or those who have had a fall
- Assessment of older adults who experience an in-hospital fall are medically examined for injury (fracture or spinal) before movement, and receive a full medical examination thereafter
- Community-dwelling older adults with a history of falls should receive a referral for strength and balance training
- A home safety assessment and appropriate interventions should be offered to older adults admitted to hospital following a fall.

**Fig. 14.1** Summary of key NICE Quality Statements 2017 – falls in older people (hospitalized) accessed at <https://www.nice.org.uk/guidance/qs86/resources/falls-in-older-people-pdf-2098911933637>

The current evidence presented here examines single and multifactorial interventions in the domains of risk assessment, exercise, medication, environment, service models, and knowledge (Table 14.3).

## Falls Risk Assessment

Over 400 risk factors have been associated with falls in hospitals [64]. A multifactorial risk assessment, which incorporates assessments by multiple health professionals, is used to target interventions most appropriate for the individual. A multitude of falls risk assessment tools can be used in hospitals, with various strengths and weaknesses. The Morse Falls Scale is most widely used in the United States, [65, 66] depicted in Fig. 14.2. In a systematic review and meta-analysis, the sensitivity and specificity of the Morse Falls Scale for predicting falls in hospitalized older adults was 72–96% and 51–83%, respectively [61].

## Exercise

Additional physiotherapy has been trialed in rehabilitation wards. In this setting, additional physiotherapy resulted in reduction in risk of falling but not in rate of falls with very low-quality evidence [67, 68]. Pooled data from all studies on falls in different settings has demonstrated a reduction in risk of injurious falls with single intervention exercise [16].

**Table 14.3** Interventions in hospitals to reduce falls

	Single	Multifactorial
Additional physiotherapy (on rehab wards)	No effect on rate Decreased risk	
Vitamin D and calcium	No effect on risk	
Environment	Increased rate	
Carpeted floors	No effect	
Low-low beds	No effect	
Exit alarms	No effect	
Bracelets		
Service model	No effect	
Change		
Knowledge	Mixed effect (none or reduced rate)	
Training staff	Reduced rate of falls in cognitively intact	
Educating patients		
Multifactorial		Reduced rate
Hip protectors, information, exercise, education		
Orthogeriatric and multidisciplinary care		Reduced rate and risk
Delirium prevention based on HELP model		Reduced rate
Mobility Twice-daily assisted ambulation and behavioral strategies		Trend toward reduced rate

*HELP* Hospital Elder Life Program

## Medication

Supplemental vitamin D 800 IU and 1200 mg calcium was examined in patients with a median length of stay of 30 days. No effect was observed on risk of falling [69]. Additional medication interventions have been studied as a component of multifactorial interventions, rather than single interventions, and will be discussed elsewhere. A study examining the effect of a multi-professional medication review did not demonstrate an effect of risk of falling or rate of falls after adjustment for clustering [70].

## Environment

Carpeted floors in rehabilitation wards have been found to increase the rate of falls but not the risk of falling [65]. The theoretical increased risk of fractures on vinyl floors, as opposed to carpeted floors, has not been observed in the reviewed literature.

Low-low beds are hospital beds that can sit directly apposed to the floor and can be elevated when required. The implementation of a low-low bed policy in a single-center study did not demonstrate a reduction in rate of falls or associated injuries [71].

Variable	Numeric Value	
1. History of falling	No	0
	Yes	25
2. Secondary diagnosis	No	0
	Yes	15
3. Ambulatory aid		
Non/bed rest/nurse assist		0
Crutches/cane/walker		15
Furniture		30
4. IV or IV access	No	0
	Yes	20
5. Gait		
Normal/bed rest/wheelchair		0
Weak		10
Impaired		20
6. Mental status		
	Orientated to own ability	0
	Overestimates or forgets limitations	15
Morse Falls Scale Score	Total	
Interpretation		
No risk < 25		
Moderate risk 26 – 45		
High risk >46		

Fig. 14.2 Morse Falls Scale

Other environmental interventions, including identifying bracelets and exit alarms, have not demonstrated an effect on rate of falls in hospitals [72, 73]. A strategy designed to increase bed alarm use across hospitals found no reduction in rate of falls or injurious falls, but increased alarm use and possible stress among nursing staff [74]. A study which enrolled participants who required assistance with

mobilizing and installed bed alarms did not show reductions in risk of falling or rate of falls [75]. Alarms have been criticized for their restrictive nature and reduction in patient mobility [62].

## **Service Model Change**

Multiple, specific service models have been examined for impact on rate of falls and risk of falling. Hospital models studied include a computer-based fall prevention kit, acute-aged care units, and a behavioral advisory service for patients with delirium. All models demonstrated no effect on rate of falls [76–78].

## **Knowledge**

Education and training interventions have shown mixed results in reducing the rate of falls and risk of falling in hospitals. Training nursing and allied health staff in targeted guideline implementation demonstrated no effect on rate of falls [79, 80]. However, a large cohort educated by a trained research nurse on targeting falls risk factors in high-risk patients demonstrated a significant reduction in risk of falling [81]. The provision of education to inpatients on falls risk reduction, which included video- and text-based material in addition to one-on-one follow-up for the intervention group, demonstrated no effect on rate of falls [82]. However, on post-hoc analysis it was revealed that in those who had intact cognition and received the complete program, a reduction in rate of falls was observed [82].

## **Multifactorial Interventions**

A number of studies have examined multifactorial interventions, all of which consisted of different components. Two combinations of interventions demonstrated a reduction in rate of falls. The first, in a study by Haines et al., provided individually targeted interventions on subacute hospital wards. The components were falls risk alert card, information brochure, hip protectors, exercise, and education programs [83]. Rate of falls were reduced but not risk of falling and the benefit was most evident in those who were inpatients for greater than 45 days [84].

The orthogeriatric model of care, which comprises a comprehensive geriatric assessment and falls risk assessment by the multidisciplinary team, has been shown to reduce rate of falls and risk of falling when compared to usual, orthopedic team care [85]. Two studies, comparing multifactorial (medical, behavioral, cognitive, and environmental modifications) on rehabilitation wards and medical surgical wards, respectively, did not show any effect of rate of falls [86, 87].



## Delirium Prevention and Mobility

Multicomponent and nonpharmacological programs targeting prevention of delirium have demonstrated a reduction in rate of falls and delirium incidence in hospitalized older people, in addition with a trend toward reduction in length of stay and institutionalization [88]. The origin of this multicomponent approach is the Hospital Elder Life Program (HELP), which is widely used in the United States [89–91]. The HELP program involves screening all patients aged 70 years or over for 6 key risk factors, which include cognitive impairment, sleep deprivation, immobility, dehydration, vision, or hearing impairment [90]. Targeted interventions addressing identified risk factors are implemented by an interdisciplinary team and reviewed twice-weekly at interdisciplinary rounds [90]. The findings of a recent meta-analysis indirectly highlight the association between cognition and mobility by demonstrating a reduction in falls with this program [91]. Also suggested is that a focus on cognition, rather than directly on falls, may have positive effects on falls reduction [91].

Hospital mobility programs, which comprise assistance with ambulation twice daily and behavioral interventions to encourage mobility, have demonstrated a trend toward falls reduction [92]. Despite not reaching statistical significance for reduction in falls rate, patients were more likely to maintain their pre-hospital function and mobility on discharge back to the community [92].

---

## Conclusion

Falls in nursing home residents and hospitalized older people will continue to pose challenges for individuals and society for years to come. While evidence is building for falls prevention strategies, it remains limited. Despite these limitations, areas with the strongest evidence for falls reduction include risk identification and targeted intervention, exercise programs in the specific demographics, vitamin D supplementation in deficient nursing home residents, interdisciplinary management in patients with hip fracture, and multicomponent delirium prevention in hospitalized older people.

---

## References

1. Gill TM, Murphy TE, Gahbauer EA, Allore HG. Association of injurious falls with disability outcomes and nursing home admissions in community-living older persons. *Am J Epidemiol*. 2013;178(3):418–25.
2. Siracuse JJ, Odell DD, Gondek SP, et al. Health care and socioeconomic impact of falls in the elderly. *Am J Surg*. 2012;203(3):335–8.
3. Kumar A, Carpenter H, Morris R, et al. Which factors are associated with fear of falling in community-dwelling older people? *Age Ageing*. 2014;43(1):76–84.
4. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults - United States. *J Saf Res*. 2016;58:99–103.

5. Nurmi I, Luthje P. Incidence and costs of falls and fall injuries among elderly in institutional care. *Scand J Prim Health Care*. 2002;20(2):118–22.
6. Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. *Ann Int Med*. 1994;121(6):442–51.
7. Nyberg L, Gustafson Y, Janson A, et al. Incidence of falls in three different types of geriatric care. A Swedish prospective study. *Scand J Social Med*. 1997;25(1):8–13.
8. Rapp K, Becker C, Cameron ID, et al. Epidemiology of falls in residential aged care: analysis of more than 70,000 falls from residents of Bavarian nursing homes. *J Am Med Dir Assoc*. 2012;13(2):187.e1–6.
9. Lord SR, March LM, Cameron ID, et al. Differing risk factors for falls in nursing home and intermediate-care residents who can and cannot stand unaided. *J Am Geriatr Soc*. 2003;51(11):1645–50.
10. Oliver D, Daly F, Martin FC, McMurdo ME. Risk factors and risk assessment tools for falls in hospital in-patients: a systematic review. *Age Ageing*. 2004;33(2):122–30.
11. Vieira ER, Freund-Heritage R, da Costa BR. Risk factors for geriatric patient falls in rehabilitation hospital settings: a systematic review. *Clin Rehabil*. 2011;25(9):788–99.
12. Chartered Society of Physiotherapy. Falls prevention economic model. <http://www.Csp.Org.Uk/professional-union/practice/your-business/evidence-base/cost-falls>. Accessed 15 Jan 2018.
13. Kojima G, Kendrick D, Skelton DA, et al. Frailty predicts short-term incidence of future falls among british community-dwelling older people: a prospective cohort study nested within a randomised controlled trial. *BMC Geriatr*. 2015;15:155.
14. Cooper R. Reducing falls in a care home. *BMJ Qual Improv Rep*. 2017;6(1):u214186.w5626.
15. Cameron ID, Dyer SM, Panagoda CE, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Datab Sys Rev*. 2018;(9):Cd005465.
16. Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. *JAMA*. 2017;318(17):1687–99.
17. Shimada H, Obuchi S, Furuta T, Suzuki T. New intervention program for preventing falls among frail elderly people: the effects of perturbed walking exercise using a bilateral separated treadmill. *Am J Phys Med Rehabil*. 2004;83(7):493–9.
18. Sihvonen S, Sipila S, Taskinen S, Era P. Fall incidence in frail older women after individualized visual feedback-based balance training. *Gerontol*. 2004;50(6):411–6.
19. Sakamoto K, Nakamura T, Hagino H, et al. Effects of unipedal standing balance exercise on the prevention of falls and hip fracture among clinically defined high-risk elderly individuals: a randomized controlled trial. *J Orthop Sci*. 2005;11(5):467–72.
20. Faber MJ, Bosscher RJ, Chin APMJ, van Wieringen PC. Effects of exercise programs on falls and mobility in frail and pre-frail older adults: a multicenter randomized controlled trial. *Arch Phys Med Rehabil*. 2006;87(7):885–96.
21. Kerse N, Peri K, Robinson E, et al. Does a functional activity programme improve function, quality of life, and falls for residents in long term care? Cluster Randomised Controlled Trial. *BMJ*. 2008;337:a1445.
22. Choi JH, Moon JS, Song R. Effects of sun-style tai chi exercise on physical fitness and fall prevention in fall-prone older adults. *J Advanc Nurs*. 2005;51(2):150–7.
23. Nowalk MP, Prendergast JM, Bayles CM, et al. A randomized trial of exercise programs among older individuals living in two long-term care facilities: the fallsfree program. *J Am Geriatr Soc*. 2001;49(7):859–65.
24. Mulrow CD, Gerety MB, Kanten D, et al. Effects of physical therapy on functional status of nursing home residents. *J Am Geriatr Soc*. 1993;41(3):326–8.
25. Littbrand H, Carlsson M, Lundin-Olsson L, et al. Effect of a high-intensity functional exercise program on functional balance: preplanned subgroup analyses of a randomized controlled trial in residential care facilities. *J Am Geriatr Soc*. 2011;59(7):1274–82.
26. Schoenfelder DP. A fall prevention program for elderly individuals. Exercise in long-term care settings. *J Gerontol Nurs*. 2000;26(3):43–51.

27. Serra-Rexach JA, Bustamante-Ara N, Hierro Villaran M, et al. Short-term, light- to moderate-intensity exercise training improves leg muscle strength in the oldest old: a randomized controlled trial. *J Am Geriatr Soc.* 2011;59(4):594–602.
28. Toulotte C, Fabre C, Dangremont B, et al. Effects of physical training on the physical capacity of frail, demented patients with a history of falling: a randomised controlled trial. *Age Ageing.* 2003;32(1):67–73.
29. Crotty M, Rowett D, Spurling L, et al. Does the addition of a pharmacist transition coordinator improve evidence-based medication management and health outcomes in older adults moving from the hospital to a long-term care facility? Results of a randomized, controlled trial. *Am J Geriatr Pharmacother.* 2004;2(4):257–64.
30. Lapane KL, Hughes CM, Daiello LA, et al. Effect of a pharmacist-led multicomponent intervention focusing on the medication monitoring phase to prevent potential adverse drug events in nursing homes. *J Am Geriatr Soc.* 2011;59(7):1238–45.
31. Zermansky AG, Alldred DP, Petty DR, et al. Clinical medication review by a pharmacist of elderly people living in care homes—randomised controlled trial. *Age Ageing.* 2006;35(6):586–91.
32. Patterson SM, Hughes CM, Crealey G, et al. An evaluation of an adapted US model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in northern Ireland. *J Am Geriatr Soc.* 2010;58(1):44–53.
33. Wallerstedt SM, Kindblom JM, Nylen K, et al. Medication reviews for nursing home residents to reduce mortality and hospitalization: systematic review and meta-analysis. *Br J Clin Pharmacol.* 2014;78(3):488–97.
34. Holick MF. Vitamin d deficiency. *New Eng J Med.* 2007;357(3):266–81.
35. DeLuca GC, Kimball SM, Kolasinski J, et al. Review: the role of vitamin d in nervous system health and disease. *Neuropathol Appl Neurobiol.* 2013;39(5):458–84.
36. Feron F, Burne TH, Brown J, et al. Developmental vitamin d3 deficiency alters the adult rat brain. *Brain Res Bull.* 2005;65(2):141–8.
37. Tomlinson PB, Joseph C, Angioi M. Effects of vitamin d supplementation on upper and lower body muscle strength levels in healthy individuals. A systematic review with meta-analysis. *J Sci Med Sport.* 2015;18(5):575–80.
38. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin d and calcium supplementation on falls: a randomized controlled trial. *J Bone Min Res.* 2003;18(2):343–51.
39. Broe KE, Chen TC, Weinberg J, et al. A higher dose of vitamin d reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc.* 2007;55(2):234–9.
40. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin d3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the decalys II study. *Osteoporos Int.* 2002;13(3):257–64.
41. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin d to prevent falls? Results of a randomized trial. *J Am Geriatr Soc.* 2005;53(11):1881–8.
42. Law M, Withers H, Morris J, Anderson F. Vitamin d supplementation and the prevention of fractures and falls: results of a randomised trial in elderly people in residential accommodation. *Age Ageing.* 2006;35(5):482–6.
43. Grieger JA, Nowson CA, Jarman HF, et al. Multivitamin supplementation improves nutritional status and bone quality in aged care residents. *Eur J Clin Nutr.* 2009;63(4):558–65.
44. Cox H, Puffer S, Morton V, et al. Educating nursing home staff on fracture prevention: a cluster randomised trial. *Age Ageing.* 2008;37(2):167–72.
45. Meyer G, Kopke S, Haastert B, Muhlhauser I. Comparison of a fall risk assessment tool with nurses' judgement alone: a cluster-randomised controlled trial. *Age Ageing.* 2009;38(4):417–23.
46. Ward JA, Harden M, Gibson RE, Byles JE. A cluster randomised controlled trial to prevent injury due to falls in a residential aged care population. *Med J Aust.* 2010;192(6):319–22.
47. Chenoweth L, King MT, Jeon YH, et al. Caring for aged dementia care resident study (cades) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial. *Lancet Neurol.* 2009;8(4):317–25.

48. Huang TT, Chung ML, Chen FR, et al. Evaluation of a combined cognitive-behavioural and exercise intervention to manage fear of falling among elderly residents in nursing homes. *Aging Ment Health*. 2016;20(1):2–12.
49. van het Reve E, de Bruin ED. Strength-balance supplemented with computerized cognitive training to improve dual task gait and divided attention in older adults: a multicenter randomized-controlled trial. *BMC Geriatr*. 2014;14:134.
50. Bates-Jensen BM, Alessi CA, Al-Samarrai NR, Schnelle JF. The effects of an exercise and incontinence intervention on skin health outcomes in nursing home residents. *J Am Geriatr Soc*. 2003;51(3):348–55.
51. Durvasula S, Kok C, Sambrook PN, et al. Sunlight and health: attitudes of older people living in intermediate care facilities in southern Australia. *Arch Gerontol Geriatr*. 2010;51(3):e94–9.
52. Becker C, Kron M, Lindemann U, et al. Effectiveness of a multifaceted intervention on falls in nursing home residents. *J Am Geriatr Soc*. 2003;51(3):306–13.
53. Dyer CA, Taylor GJ, Reed M, et al. Falls prevention in residential care homes: a randomised controlled trial. *Age Ageing*. 2004;33(6):596–602.
54. Jensen J, Lundin-Olsson L, Nyberg L, Gustafson Y. Fall and injury prevention in older people living in residential care facilities. A cluster randomized trial. *Ann Int Med*. 2002;136(10):733–41.
55. Kerse N, Butler M, Robinson E, Todd M. Fall prevention in residential care: a cluster, randomized, controlled trial. *J Am Geriatr Soc*. 2004;52(4):524–31.
56. McMurdo ME, Millar AM, Daly F. A randomized controlled trial of fall prevention strategies in old peoples' homes. *Gerontol*. 2000;46(2):83–7.
57. Neyens JC, Dijcks DP, Twisk J, et al. A multifactorial intervention for the prevention of falls in psychogeriatric nursing home patients, a randomised controlled trial (RCT). *Age Ageing*. 2009;38(2):194–9.
58. Ray WA, Taylor JA, Meador KG, et al. A randomized trial of a consultation service to reduce falls in nursing homes. *JAMA*. 1997;278(7):557–62.
59. Rubenstein LZ, Robbins AS, Josephson KR, et al. The value of assessing falls in an elderly population. A randomized clinical trial. *Ann Int Med*. 1990;113(4):308–16.
60. Shaw FE, Bond J, Richardson DA, et al. Multifactorial intervention after a fall in older people with cognitive impairment and dementia presenting to the accident and emergency department: randomised controlled trial. *BMJ*. 2003;326(7380):73.
61. Hempel S, Newberry S, Wang Z, et al. Hospital fall prevention: a systematic review of implementation, components, adherence, and effectiveness. *J Am Ger Soc*. 2013;61(4):483–94.
62. Growdon ME, Shorr RI, Inouye SK. The tension between promoting mobility and preventing falls in the hospital. *JAMA Int Med*. 2017;177(6):759–60.
63. Brown CJ, Redden DT, Flood KL, Allman RM. The underrecognized epidemic of low mobility during hospitalization of older adults. *J Am Geriatr Soc*. 2009;57(9):1660–5.
64. National Institute of Clinical Excellence. Falls in older people. Quality standard: NICE, 2017. <https://www.nice.org.uk/guidance/qs86/resources/falls-in-older-people-pdf-2098911933637>. Accessed 16 Jan 2018.
65. Morse JM, Black C, Oberle K, Donahue P. A prospective study to identify the fall-prone patient. *Soc Sci Med*. 1989;28(1):81–6.
66. Morse JM, Morse RM, Tylko SJ. Development of a scale to identify the fall-prone patient. *Can J Aging*. 2010;8(4):366–77.
67. Donald IP, Pitt K, Armstrong E, Shuttleworth H. Preventing falls on an elderly care rehabilitation ward. *Clin Rehabil*. 2000;14(2):178–85.
68. Jarvis N, Kerr K, Mockett S. Pilot study to explore the feasibility of a randomised controlled trial to determine the dose effect of physiotherapy on patients admitted to hospital following a fall. *Prac Evid*. 2007;2(2):4–12.
69. Burleigh E, McColl J, Potter J. Does vitamin d stop inpatients falling? A randomised controlled trial. *Age Ageing*. 2007;36(5):507–13.
70. Michalek C, Wehling M, Schlitzer J, et al. Effects of “Fit fOR The Aged” (FORTA) on pharmacotherapy and clinical endpoints - a pilot randomized controlled study. *Eur J Clin Pharm*. 2014;70(10):1261–7.

71. Haines TP, Bell RA, Varghese PN. Pragmatic, cluster randomized trial of a policy to introduce low-low beds to hospital wards for the prevention of falls and fall injuries. *J Am Geriatr Soc*. 2010;58(3):435–41.
72. Mayo NE, Gloutney L, Levy AR. A randomized trial of identification bracelets to prevent falls among patients in a rehabilitation hospital. *Arch Phys Med Rehabil*. 1994;75(12):1302–8.
73. Tideiksaar R, Feiner CF, Maby J. Falls prevention: the efficacy of a bed alarm system in an acute-care setting. *Mt Sin J Med*. 1993;60(6):522–7.
74. Shorr RI, Chandler AM, Mion LC, et al. Effects of an intervention to increase bed alarm use to prevent falls in hospitalized patients: a cluster randomized trial. *Ann Int Med*. 2012;157(10):692–9.
75. Wolf KH, Hetzer K, Zu Schwabedissen HM, Wiese B, et al. Development and pilot study of a bed-exit alarm based on a body-worn accelerometer. *Z Gerontol Geriatr*. 2013;46(8):727–33.
76. Dykes PC, Carroll DL, Hurley A, et al. Fall prevention in acute care hospitals: a randomized trial. *JAMA*. 2010;304(17):1912–8.
77. Wald HL, Glasheen JJ, Guerrasio J, et al. Evaluation of a hospitalist-run acute care for the elderly service. *J Hosp Med*. 2011;6(6):313–21.
78. Mador JE, Giles L, Whitehead C, Crotty M. A randomized controlled trial of a behavior advisory service for hospitalized older patients with confusion. *Int J Geriatr Psychiatry*. 2004;19(9):858–63.
79. Koh SL, Hafizah N, Lee JY, et al. Impact of a fall prevention programme in acute hospital settings in Singapore. *Singap Med J*. 2009;50(4):425–32.
80. van Gaal BG, Schoonhoven L, Mintjes JA, et al. The safe or sorry? Programme. Part ii: Effect on preventive care. *Int J Nurs Stud*. 2011;48(9):1049–57.
81. Ang E, Mordiffi SZ, Wong HB. Evaluating the use of a targeted multiple intervention strategy in reducing patient falls in an acute care hospital: a randomized controlled trial. *J Adv Nurs*. 2011;67(9):1984–92.
82. Haines TP, Hill AM, Hill KD, et al. Patient education to prevent falls among older hospital inpatients: a randomized controlled trial. *Arch Int Med*. 2011;171(6):516–24.
83. Haines TP, Bennell KL, Osborne RH, Hill KD. Effectiveness of targeted falls prevention programme in subacute hospital setting: randomised controlled trial. *BMJ*. 2004;328(7441):676.
84. Stenvall M, Olofsson B, Lundstrom M, et al. A multidisciplinary, multifactorial intervention program reduces postoperative falls and injuries after femoral neck fracture. *Osteoporos Int*. 2007;18(2):167–75.
85. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Int Med*. 2015;175(4):512–20.
86. Aizen E, Lutsyk G, Wainer L, Carmeli S. Effectiveness of individualized fall prevention program in geriatric rehabilitation hospital setting: a cluster randomized trial. *Aging Clin Exp Res*. 2015;27(5):681–8.
87. Barker AL, Morello RT, Ayton DR, et al. Development of an implementation plan for the 6-PACK falls prevention programme as part of a randomised controlled trial: protocol for a series of preimplementation studies. *Inj Prevent*. 2016;22(6):446–52.
88. Inouye SK, Bogardus ST, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *New Eng J Med*. 1999;340(9):669–76.
89. Inouye SK, Bogardus ST, Baker DI, et al. The hospital elder life program: a model of care to prevent cognitive and functional decline in older hospitalized patients. Hospital elder life program. *J Am Geriatr Soc*. 2000;48(12):1697–706.
90. Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. *Ann Med*. 2000;32(4):257–63.
91. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multi-component non-pharmacologic delirium interventions: a meta-analysis. *JAMA Int Med*. 2015;175(4):512–20.
92. Brown CJ, Foley KT, Lowman JD, et al. Comparison of posthospitalization function and community mobility in hospital mobility program and usual care patients: a randomized clinical trial. *JAMA Int Med*. 2016;176(7):921–7.

---

## **Part IV**

# **Prevention and Interventions**



# Evidence, Recommendations, and Current Gaps in Guidelines for Fall Prevention and Treatments

# 15

Susan W. Hunter and Mark Speechley

---

## Introduction

Clinical practice guidelines (CPGs) provide systematically developed recommendations to assist clinicians in the care of patients with specific conditions. The recommendations are based on carefully conducted systematic reviews of the available research evidence, allowing the recommendations to be presented in terms of both their strength (e.g., weak to strong) and the quality of the underlying evidence (low to high). Guidelines are a starting place for decision making that are then modified based on clinical judgement about individual patients as well as the preferences and values of those patients. Clinical practice guidelines are expected to facilitate more consistent, effective, and efficient medical practice, and improve health outcomes for the relevant patient population of interest [1].

While several clinical practice guidelines for falls prevention have been published, none have been geared to the specific population of older adults living with cognitive impairment. The objectives of this chapter are to briefly review the history of fall prevention guidelines, identify the role of cognitive status in those guidelines, and identify gaps in current knowledge that impede the creation of a specific fall prevention CPG for those with cognitive impairment.

---

S. W. Hunter (✉)

School of Physical Therapy, University of Western Ontario, London, ON, Canada  
e-mail: [susan.hunter@uwo.ca](mailto:susan.hunter@uwo.ca)

M. Speechley

Department of Epidemiology & Biostatistics, Schulich School of Medicine & Dentistry,  
University of Western Ontario, London, ON, Canada  
e-mail: [speechley@uwo.ca](mailto:speechley@uwo.ca)

© Springer Nature Switzerland AG 2020

M. Montero-Odasso, R. Camicioli (eds.), *Falls and Cognition in Older Persons*,  
[https://doi.org/10.1007/978-3-030-24233-6\\_15](https://doi.org/10.1007/978-3-030-24233-6_15)

263

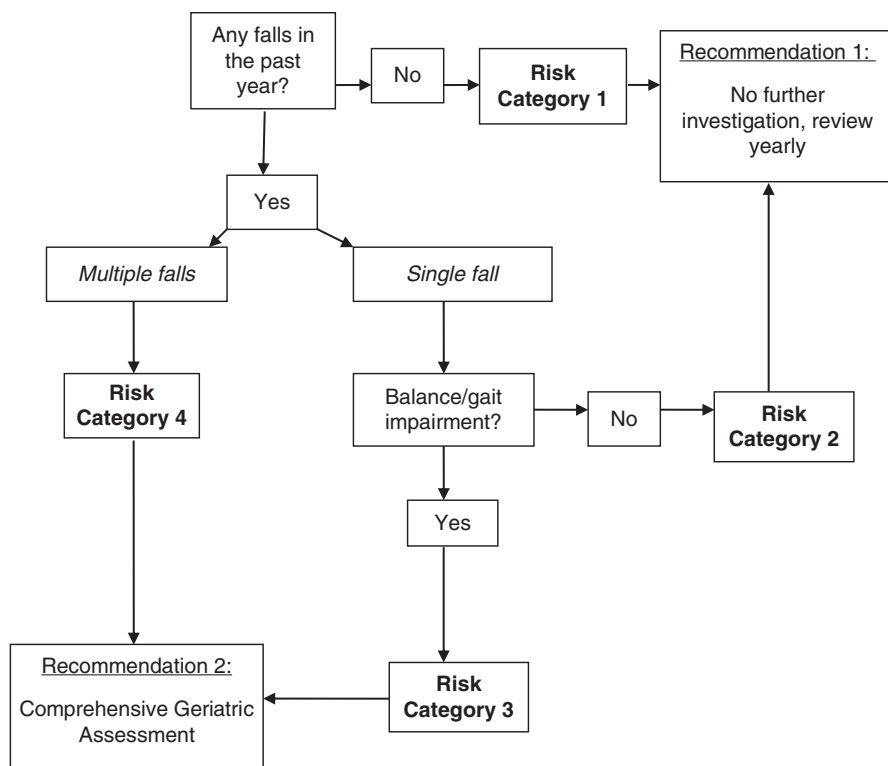


## Development of Early Falls Prevention Clinical Practice Guidelines

The synthesis of the growing body of research on fall risk factors into fall risk screening and assessment algorithms and falls prevention strategies in older adults across care and living situations has been an area of focus for clinical practice guidelines since the early 2000s. The first prospective epidemiological studies on risk factors for falls in older adults were published in the late 1980s [2, 3]. These ushered in an era of research to understand falls in older adults by summarizing knowledge about risk and protective factors for falls [4] and evaluating their modifiability in randomized controlled studies of a myriad of falls prevention strategies [5, 6]. Clinical practice guidelines for falls prevention in older adults facilitate knowledge translation to frontline clinicians of the vast body of research that developed in the past 30 years to optimize the delivery of evidence-based clinical care.

The first and highest profile set of clinical practice guidelines for the prevention of falls in older adults were published by the American Geriatrics Society and the British Geriatrics Society in 2001 [7]. An important contribution of this paper was an algorithm, based on evidence in the literature for risk factors and associations with future falls risk. (Fig. 15.1) The algorithm contained recommendations for both fall risk screening and fall risk assessment. The concept of screening as applied to injury prevention consists of the rapid identification of people who are probably likely to fall, and those who are probably not likely to fall, over a future time period such as a year. The algorithm's screening step was designed as periodic case finding in primary care encounters and consisted of taking a one-year falls history in all patients. If the person reported no falls (screen negative, Risk Category 1), then the recommendation was yearly re-screening. Those who screened positive on recent fall history were then streamed to two groups for subsequent assessment according to whether they reported a single fall or multiple falls. In people reporting a single fall, the recommendation was an assessment for balance or gait problems. If there were no identified balance or gait problems, the recommendation was yearly re-screening (Risk Category 2). One-time fallers with identified balance or gait problems were streamed to a comprehensive geriatric assessment (Risk Category 3). Finally, those who reported multiple falls in the past 12 months, as well as anyone presenting to a medical facility with an acute fall, were recommended to receive a comprehensive geriatric assessment (Risk Category 4).

The algorithm was subsequently evaluated for predictive validity for future falls [8]. The evaluation found that the algorithm was able to identify and stratify fall risk for each fall outcome, though the values of prognostic accuracy demonstrated only moderate clinical utility. Lamb et al. [9] estimated the probable accuracy of the 2001 AGS/BGS algorithm in a cohort study of 1002 community-dwelling older women who had some physical disability. Women with a Mini-Mental State Examination (MMSE) score less than 18 were ineligible and the mean (SD) MMSE for the sample was 26/30 (3.0) indicating a fairly high average level of cognitive function. Using a tree-based classification and various cut-points for walking speed, sensitivity for any fall in the next year ranged from 28% to 43% and specificity



**Fig. 15.1** Guidelines for falls prevention screening algorithm for fall risk in older adults with recommended interventions. (Figure is modified from Muir et al. [27])

ranged from 74% to 88%. The authors used MMSE scores as a continuous variable or as a cut-point of less than or equal to 24 to indicate mild-to-moderate impairment in the model, but cognitive status was not retained in any tree-based classification. The authors did not report separate calculations for the sub-sample with MMSE less than or equal to 24.

The study of the ABS/BGS screening algorithm by Muir et al. [8] found that the recommendations of a comprehensive falls evaluation for individuals in the highest risk groups was supported, though the recommendation of no confirmatory assessment in the screen negatives resulted in many missed opportunities for fall prevention interventions. It is important to highlight that the absence of a falls history in the previous 12 months does not mean a fall risk of zero, or an absence of falls risk factors. Tinetti's original prospective cohort study showed an annual fall risk of 8% even in those with zero measured risk factors and an annual fall risk of 20% in those who reported no falls in the previous 2 years [2]. Muir et al. found in community-dwelling older adults without a falls history that 27% of people fell in the subsequent 12 months and 67% had modifiable risk factors present on clinical assessment for balance problems, lower extremity weakness, and greater than four prescription medications at baseline [10].

The risk factors in the 2001 AGS/BGS guidelines were extracted from 16 studies, of which 11 assessed cognitive impairment as a risk factor. Of these studies, only four (36%) reported statistically significant crude odds or risk ratios for cognitive impairment, with a mean RR/OR of 1.8, the second smallest of 11 examined risk factors. The low end of the range of reviewed RR/OR was 1.0, indicating that cognitive impairment was associated with no increased risk of falling in some studies. However, the size of a RR/OR reflects the prevalence of a risk factor in the individual causal models present in a sample. Because people with severe and even moderate cognitive impairment were often excluded from these studies of fall risk factors, it is likely that the small and null RR/OR reflect this exclusion rather than the absence of fall risk posed by cognitive impairment. The authors noted that the cognitive status of the study samples was not reported consistently and recommended a better understanding of fall prevention in persons with cognitive impairment as a research priority. As a result of the scanty evidence, cognitive status is only briefly mentioned in the guidelines (“basic neurological function, including mental status”).

---

## **Current Status of Clinical Guidelines for Prevention of Falls in Older Adults**

As reported earlier, the 2001 AGS/BGS guidelines review of the literature only found 16 studies that assessed cognitive impairment as a falls risk factor. The systematic review by Muir et al. [11] in 2012 found 27 papers that had evaluated cognitive impairment in samples across residential settings (community-dwelling and nursing home institution) and multiple falls outcomes (any fall, recurrent falls, and injurious falls). This systematic review recommended that the method used to define cognitive impairment and the type of fall outcome are both important when quantifying falls risk. This review found that there was strong evidence that global measures of cognition were associated with serious fall-related injury, such as fractures, though there was no consensus on threshold values for common scales of global cognition (i.e., Mini-Mental State Examination) that identified an increased risk. Executive function was more consistently related with an increased falls risk across multiple categories of falls outcomes (i.e., any fall, recurrent falls, and injurious falls) than global measures of cognition. The evaluation of the cognitive domain of executive function was recommended to be used in fall risk assessment, especially when global measures are within normal limits.

An update of the American Geriatrics Society and British Geriatrics Society was published in 2011 and remains the most influential set of guidelines [12]. The updated guidelines have modified the screening step to be applied in any encounter by a health-care provider with an older adult. People screen positive if they (a) had two or more falls in the past year, (b) present with an acute fall, or (c) report difficulty with walking or balance. Initial screen negatives are then asked if they had a single fall in the past year, and those who screen negative at this second step are streamed to periodic reassessment. Those who report a single fall are to receive

balance and gait assessment, with subsequent steps based on these results. Initial screen positives receive a medical history, physical examination, functional and cognitive assessment, and assessment of multifactorial falls risk followed by appropriate interventions. Importantly, while initial screen positives are recommended to receive a cognitive assessment, the guidelines do not provide specific recommendations for this nor for evaluation of aspects of cognition that are associated with an increased falls risk, such as executive function. The guidelines therefore lack a specific intent to the assessment of cognitive function that is related to an increased falls risk; rather, the assessment has a general diagnostic intent to facilitate global health management for the older adults.

As with the original 2001 guidelines, there have been few published attempts to evaluate the performance of the updated 2011 guidelines. An exception is Palumbo et al. [13] who estimated the predictive accuracy and potential clinical consequences of the 2011 guidelines by simulating the application of the screening algorithm in a prospective cohort of 438 older adults. The cognitive status of Palumbo's sample was lower than average (i.e., MMSE of 23.1) and much more variable (SD of 7.9) than the sample Lamb et al. [9] used to evaluate the 2001 guidelines. Specifically, 27.7% had MMSE scores less than or equal to 24, indicating some cognitive impairment, and 19.2% had MMSE scores less than or equal to 18, indicative of moderate to severe impairment. In this substantially more cognitively impaired sample, 79.5% of the population would screen negative. Using a variety of cut-points for several gait and balance tests, sensitivity ranged from 33.8% to 47.8%, while the specificity ranged from 74.1% to 84.4% [13]. The authors did not report analyses separately within strata of cognitive status.

Since the 2001 version of the clinical practice guidelines, there have been other organizations that have produced their own set of guidelines, though the influence of the American Geriatrics Society and British Geriatrics Society Guidelines have remained dominant. Table 15.1 contains a listing of falls prevention clinical practice guidelines for older adults that have been published within this relevant time frame.

Importantly, there has been an emerging area of research that has specifically evaluated risk factors for falls in the cognitively impaired. Compared to our understanding of falls risk in cognitively healthy older adults, factors related to increased fall risk in people with cognitive impairment or dementia are poorly understood. Possible explanations for differences between the populations that explain the greater risk of falls in people with cognitive impairment include (a) different underlying mechanisms for risk factors that are common to both people with dementia and cognitively normal older adults, (b) the magnitudes of association for risk factors shared with cognitively normal older adults are greater, and (c) people with dementia may have unique risk factors that are not present in cognitively normal adults [14]. Additionally, the role of environmental factors as well as behaviors might be sufficiently different to warrant specific assessment and intervention approaches. As a result of insufficient evidence, fall prevention guidelines do not provide any recommendations for the population of older adults with cognitive impairment nor has there been a set of guidelines developed that are specific to people with cognitive impairment.

**Table 15.1** Clinical practice guidelines for the prevention of falls in older adults

Name of Guideline	Country	Year of Publication
American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopedic Surgeons Panel on Falls Prevention. Guideline for the Prevention of Falls in Older Persons. Journal of the American Geriatrics Society. 2001;49:664–72. ( <a href="https://doi.org/10.1046/j.1532-5415.2001.49115.x">https://doi.org/10.1046/j.1532-5415.2001.49115.x</a> )	United States and United Kingdom	2001
Strategy to falls and fractures in Ireland's aging population. Report of the National Steering Group on the Prevention of Falls in Older People and the Prevention and Management of Osteoporosis throughout Life. 2008	Ireland	2008
Preventing falls and harm from falls in older people: Best practice guidelines for Australian Community Care. Australian Commission on Safety and Quality in Health Care	Australia	2009
Preventing falls and harm from falls in older people: Best practice guidelines for Australian Hospitals. Australian Commission on Safety and Quality in Health Care.	Australia	2009
Preventing falls and harm from falls in older people: Best practice guidelines for Australian Residential Aged Care Facilities. Australian Commission on Safety and Quality in Health Care.	Australia	2009
Panel on the Prevention of Falls in Older Adults, American Geriatrics Society and British Geriatrics Society. Summary of the updated American Geriatrics Society/British Geriatrics Society Clinical Practice Guidelines for Prevention of Falls in Older Persons. Journal of the American Geriatrics Society. 2011;59(1):148–157. ( <a href="http://DOI:https://doi.org/10.1111/j.1532-5415.2010.03234.x">http:// DOI: https://doi.org/10.1111/j.1532-5415.2010.03234.x</a> )	United States, United Kingdom	2011
Beauchet O, Dubost V, Revel-Delhom C, Berrut G, Belmins J. How to manage recurrent falls in clinical practice: Guidelines for the French Society of Geriatrics and Gerontology. Journal of Nutrition and Aging. 20,011;15(1):79–84.	France	2011
Falls in older people: assessing risk and prevention. National Institute for Health and Care Excellence. ( <a href="http://nice.org.uk/guidance/cg161">nice.org.uk/guidance/cg161</a> )	United Kingdom	2013
Resource guide on falls prevention – for home care service providers. Canadian Patient Safety Institute. 2014 ( <a href="http://www.patientsafetyinstitute.ca">www.patientsafetyinstitute.ca</a> )	Canada	2014
Avin KG, Hanke TA, Kirk-Sanchez N, McDonough CM, Shubert TE, Hardage J, Hartley G, Academy of Geriatric Physical Therapy of the American Physical Therapy Association. Management of falls in community-dwelling older adults: clinical guidance statement from the Academy of Geriatric Physical Therapy of the American Physical Therapy Association. Physical therapy. 2015;95(6):815–34.	United States	2015
Clinical Best Practice Guidelines: Preventing falls and reducing injury from falls. Registered Nurses' Association of Ontario. 3rd edition. 2017 ( <a href="http://www.RNAO.ca/bpg">www.RNAO.ca/bpg</a> )	Canada	2017
Stopping Elderly Accidents, Deaths & Injuries (STEADI). US Centers for Disease Control and Prevention. ( <a href="https://www.cdc.gov/steadi/index.html">https://www.cdc.gov/steadi/index.html</a> )	United States of America	2017

## Assessment of Cognition in Falls Prevention Strategies

There is now a rich body of research establishing cognitive impairment as a prominent risk factor for falls in older adults, specifically executive function in people without a diagnosis of dementia and in people with a diagnosis of dementia [4, 11, 15]. Some clinical guidelines go beyond screening practices and include information aligned with recommendations for performing a multifactorial assessment. These types of guidelines include cognitive impairment in the list of relevant intrinsic risk factors for falls. In the guidelines that identify cognitive impairment, the use of global scales of cognition such as the Mini-Mental State Examination is recommended, along with the identification of people with an existing diagnosis of dementia. Yet, as evaluated by Muir et al. [11], the use of global scales of cognition is not supported for identification of increased falls, and therefore, clinical practice guidelines have not kept up to date with the emerging literature around testing to implement in this patient population.

Specifically, clinicians need to be aware of clinical tests that have proven reliability in people with cognitive impairment, as the cognitive impairment may adversely influence a person's ability to follow instructions of the testing procedures. The systematic review by Bossers et al. [16] provides recommended measures for the assessment of physical performance in people with dementia based on reliability and validity. Six tests were recommended from this review: Endurance capacity – 6 Minute Walk Test; Muscle Strength – Five Times Sit to Stand, 30 Second Chair Stand; Balance – Tinetti Balance Scale; and Mobility – Timed Up & Go Test and 6 Meter Walk Test [16]. The systematic review by Van Ooteghem et al. [17] provides a complete overview of assessment scales for mobility to be used in advanced dementia. Yet another systematic review by Dolotabadi et al. [18] provides a summary of balance and gait measures for the assessment of falls risk in people with dementia, though the limitation of this review, and the literature in this area in general, is a lack of prospective studies with evaluation of predictive validity of test scores on future falls. This area would benefit from further research to identify clinical assessment tools with the best diagnostic properties for associations to an increased falls risk.

Fall prevention strategies that are successful in older adults without cognitive problems have not been successful in reducing falls risk in people with cognitive impairment, although new research has begun to indicate some potential benefits [19]. The updated 2011 AGS/BGS guidelines state that there is currently insufficient evidence to recommend, for or against, single or multifactorial interventions in community-living older adults with known cognitive impairment [12]. The study by Stenvall et al. [20] implemented a comprehensive geriatric assessment and treatment of risk factors on an acute orthopedic ward for people after a femoral neck fracture found a reduction in falls and these people had better functional recovery at 4 and 12 months after surgery. In the absence of robust research for falls prevention interventions, pragmatic recommendations would be that if the mechanism by which the intervention has its effect is understood and not felt to be affected by the presence of the cognitive impairment, then it is reasonable to extrapolate

recommendations for the cognitively healthy older adult. More research is required in the area of fall prevention interventions in people with cognitive impairment and dementia.

---

## Current Gaps in Clinical Practice Guidelines

There are several gaps in current falls prevention clinical practice guidelines for older adults that should be addressed with further research. Research on falls in older adults is still a robust area of work, especially as the amount of research being done and published on falls in the cognitively impaired is increasing. Therefore, clinical practice guidelines can become out of date if not updated on a regular basis of every couple of years to capture new and emerging work on falls assessment and interventions.

There needs to be more awareness of the barriers and facilitators for health-care professionals to be able to implement falls prevention guidelines. Stenberg and Wann-Hansson [21] found compliance among health-care professionals was greater when they had experiences of a high incidence of falls with negative consequences in clients. To further improve compliance and a positive attitude among health-care professionals, a clear understanding of the benefit of clinical practice guidelines in reducing falls in older adults was needed. Additionally, facilitators to the implementation and compliance of guidelines were a supportive leadership and systematic evaluations of the clinical practice guideline outcome. Implementation challenges are present across the continuum of health-care delivery. It was found that only 3.7% of older adults who presented to an emergency department because of a fall received care consistent with the American Geriatrics Society and British Geriatrics Society guidelines [22]. More work is required in identifying and addressing barriers to the implementation of fall prevention guidelines among all health-care providers.

We also need to address negative attitudes that health-care professionals have about working with people with cognitive impairment and dementia. Research examining health-care professionals' attitudes toward working with people who have dementia has predominantly focused on medical, nursing, and social work cohorts; there is limited research among the rehabilitation profession such as physiotherapists or occupational therapists. The provision of competent care to people with dementia has been acknowledged as a global challenge for healthcare providers [23]. Negative attitudes, or at the very least non-positive attitudes, toward people with dementia have been found not only in practicing health-care professionals but also in medical [24] and nursing students [25]. Negative attitudes toward people with dementia can result in low expectations of benefit from therapy and poor patient outcomes [26]. As such, investigating factors that influence healthcare professionals' attitudes toward working with people with dementia is critical to implementing care strategies such as falls prevention.



## Conclusions

In summary, falls prevention guidelines for screening older adults do not include explicit recommendations for the evaluation for cognitive function. The assessment of cognition is among the recommendations for testing to be performed in a comprehensive multifactorial falls risk assessment. Currently, there are no falls prevention guidelines that have been specifically developed for people with cognitive impairment. More research is required in the areas of unique falls risk factors or combinations in people with cognitive impairment, effective falls prevention interventions for people with cognitive impairment, rigorous prospective evaluations of falls prevention guidelines, better strategies to facilitate health-care professionals' implementation of falls prevention guidelines, and education programs to address negative attitudes among health-care professionals working with people with cognitive impairment or dementia.

## References

1. AGREE. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Heal Care*. 2003;12(1):18–23. <https://doi.org/10.1136/qhc.12.1.18>.
2. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319(26):1701–7.
3. Campbell A, Borrie M, Spears G. Risk factors for falls in a community-based prospective study of people 70 years and older. *Journals Gerontol - Ser A Biol Sci Med Sci*. 1989;44(4):M112–7.
4. Deandrea S, Lucenteforte E, Bravi FF, Foschi R, La Vecchia C, Negri E. Risk factors for falls in community-dwelling older people: a systematic review and meta-analysis. *Epidemiology*. 2010;21(5):658–68. <https://doi.org/10.1097/EDE.0b013e3181e89905>.
5. Hopewell S, Adedire O, Copsey B, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community (Review). *Cochrane Database Syst Rev*. 2018;(7):CD012221. <https://doi.org/10.1002/14651858.CD012221.pub2>. [www.cochranelibrary.com](http://www.cochranelibrary.com).
6. Cameron L, Dyer S, Panagoda C, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev*. 2018;(12, 9):CD005465. <https://doi.org/10.1002/14651858.CD005465.pub4>. [www.cochranelibrary.com](http://www.cochranelibrary.com).
7. American Geriatrics Society. British geriatrics society, American Academy of Orthopaedic surgeons panel on falls prevention. Guideline for the prevention of falls in older persons. *J Am Geriatr Soc*. 2001;49(5):664–72. <https://doi.org/10.1046/j.1532-5415.2001.49115.x>.
8. Muir SW, Berg K, Chesworth B, Klar N, Speechley M. Application of a fall screening algorithm stratified fall risk but missed preventive opportunities in community-dwelling older adults: a prospective study. *J Geriatr Phys Ther*. 2010;33(4):165–72. <https://doi.org/10.1097/JPT.0b013e3181ff23cc>.
9. Lamb SE, McCabe C, Becker C, Fried LP, Guralnik JM. The optimal sequence and selection of screening test items to predict fall risk in older disabled women: the Women's health and aging study. *Journals Gerontol*. 2008;63(10):1082–8. <https://doi.org/10.1093/gerona/63.10.1082>.
10. Muir SW, Berg K, Chesworth BM, Klar N, Speechley M. Modifiable risk factors identify people who transition from non-fallers to fallers in community-dwelling older adults: a prospective study. *Physiother Can*. 2010;62(4):358–67. <https://doi.org/10.3138/physio.62.4.358>.

11. Muir S, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299–308. <https://doi.org/10.1093/ageing/afs012>.
12. Panel for Prevention of Falls in Older Adults, American Geriatrics Society, Society BG. Summary of the updated American Geriatrics Society/British geriatrics society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc*. 2011;59(1):148–57. <https://doi.org/10.1111/j.1532-5415.2010.03234.x>.
13. Palumbo P, Becker C, Bandinelli S, Chiari L. Simulating the effects of a clinical guidelines screening algorithm for fall risk in community dwelling older adults. *Aging Clin Exp Res*. 2018; <https://doi.org/10.1007/s40520-018-1051-5>.
14. Shaw FE. Prevention of falls in older people with dementia. *J Neural Transm*. 2007;114(10):1259–64. <https://doi.org/10.1007/s00702-007-0741-5>.
15. Fernando E, Fraser M, Hendriksen J, Kim CH, Muir-Hunter SW. Risk factors associated with falls in older adults with dementia: a systematic review. *Physiother Canada*. 2017;69(2):161–70. <https://doi.org/10.3138/ptc.2016-14>.
16. Bossers WJR, van der Woude LHV, Boersma F, Scherder EJA, van Heuvelen MJG. Recommended measures for the assessment of cognitive and physical performance in older patients with dementia: a systematic review. *Dement Geriatr Cogn Dis Extra*. 2012;2(1):589–609. <https://doi.org/10.1159/000345038>.
17. Van Ooteghem K, Musselman K, Gold D, et al. Evaluating mobility in advanced dementia: a scoping review and feasibility analysis. *Gerontology*. 2018;29:1–14. [https://doi.org/10.1016/0038-1098\(79\)91043-3](https://doi.org/10.1016/0038-1098(79)91043-3).
18. Dolatabadi E, Van Ooteghem K, Taati B, Iaboni A. Quantitative mobility assessment for fall risk prediction in dementia: a systematic review. *Dement Geriatr Cogn Disord*. 2018;45(5–6):353–67. <https://doi.org/10.1159/000490850>.
19. Burton E, Cavalheri V, Adams R, et al. Effectiveness of exercise programs to reduce falls in older people with dementia living in the community: a systematic review and meta-analysis. *Clin Interv Aging*. 2015;10:421–34. <https://doi.org/10.2147/CIA.S71691>.
20. Stenvall M, Olofsson B, Lundström M, et al. A multidisciplinary, multifactorial intervention program reduces postoperative falls and injuries after femoral neck fracture. *Osteoporos Int*. 2007;18(2):167–75. <https://doi.org/10.1007/s00198-006-0226-7>.
21. Stenberg M, Wann-Hansson C. Health care professionals' attitudes and compliance to clinical practice guidelines to prevent falls and fall injuries. *Worldviews Evidence-Based Nurs*. 2011;8(2):87–95. <https://doi.org/10.1111/j.1741-6787.2010.00196.x>.
22. Salter AE, Khan KM, Donaldson MG, et al. Community-dwelling seniors who present to the emergency department with a fall do not receive guideline care and their fall risk profile worsens significantly: a 6-month prospective study. *Osteoporos Int*. 2006;17(5):672–83. <https://doi.org/10.1007/s00198-005-0032-7>.
23. Doyle C. International perspectives on dementia education, training and knowledge transfer. *Int Psychogeriatrics*. 2009;21:S1–2.
24. Tullo E, Allan L. What should we be teaching medical students about dementia? *Int Psychogeriatrics*. 2011;23(7):1044–50. <https://doi.org/10.1017/S1041610211000536>.
25. Eccleston CEA, Lea EJ, McInerney F, Crisp E, Marlow A, Robinson AL. An investigation of nursing students' knowledge of dementia: a questionnaire study. *Nurse Educ Today*. 2015;35(6):800–5. <https://doi.org/10.1016/j.nedt.2015.02.019>.
26. Staples W, Killian C. Development of an instrument to measure attitudes of physical therapy providers working with people with dementia. *Am J Alzheimers Dis Other Dement*. 2012;27(5):331–8.
27. Muir SW, Berg K, Chesworth B, Klar N, Speechley M. Application of a fall screening algorithm stratified fall risk but missed preventive opportunities in community-dwelling older adults: a prospective study. *J Geriatr Phys Ther*. 2010;33:165–72.



# Exercise to Prevent Falls in Older Adults with Cognitive Impairment

# 16

Teresa Liu-Ambrose, Jennifer C. Davis, and Chun Liang Hsu

## Introduction

Maintenance of mobility is important in older adults as it is vital to healthy aging, functional independence, and quality of life. Mobility generally comprises of all types of movement that constitute the basic form of ambulation, whereby optimal mobility is characterized by the capacity to traverse across any terrain in a reliable and safe fashion [1]. Impaired mobility is a major concern for older adults and is associated with increased risk for disability, institutionalization, and death [2]. The prevalence of impaired mobility is 14% at age 75 years and includes half of the population over 84 years [3]. More specifically, the Center for Disease Control and Prevention reported approximately 31.7% of older adults over the age of 65 experience difficulties in walking up to three city blocks [4]. Falls are a significant consequence of impaired mobility, 20% of falls require medical attention, 5% result in fracture, and one-third of those results in a fractured hip – a particular consequence of falls that is associated with high morbidity and mortality [3]. Hence, falls place a major and increasing demand on the public health system.

---

T. Liu-Ambrose (✉) · C. L. Hsu

Aging, Mobility, and Cognitive Neuroscience Lab, University of British Columbia, Vancouver, BC, Canada

Department of Physical Therapy, University of British Columbia, Vancouver, BC, Canada

Djavad Mowafaghian Center for Brain Health, University of British Columbia, Vancouver, BC, Canada

Center for Hip Health and Mobility, Vancouver, BC, Canada

e-mail: [teresa.ambrose@ubc.ca](mailto:teresa.ambrose@ubc.ca); [liang.hsu@hiphealth.ca](mailto:liang.hsu@hiphealth.ca)

J. C. Davis

Center for Hip Health and Mobility, Vancouver, BC, Canada

Faculty of Management, University of British Columbia Okanagan, Kelowna, BC, Canada

e-mail: [jennifer.davis@ubc.ca](mailto:jennifer.davis@ubc.ca)

Fortunately, falls are not random events and can be prevented. For the general population of community-dwelling older adults, there is Level 1 evidence [5] that targeted exercise training is an effective intervention strategy [6]. Evidence from 88 randomized controlled trials (with 19,478 participants) demonstrates exercise can reduce the rate of falls in community-dwelling older people by 21% with greater effects observed from exercise programs that target balance and have higher doses [7].

Specifically, the Otago Exercise Program (OEP) – a physical therapist-delivered, progressive home-based strength and balance training program tailored for older adults – is the exercise training program with the strongest evidence for falls prevention in older adults [6]. The Cochrane Collaboration [6] explicitly identifies the OEP as the exercise training program with the strongest evidence for falls reduction. Further, the OEP is cost-saving (i.e., effective and saves health care system dollars) in people  $\geq 80$  years [8]. However, there remains a lack of consistent evidence for fall prevention in older adults with cognitive impairment – a population at high-risk for falls – an area increasingly recognized as a research priority.

---

## Cognitive Function and Falls

The classical theoretical model suggests mobility deficits arise as a consequence of physiological abnormalities or alterations that occur with old age [9]. This negatively impacts the functions of various biological systems, and thereby, leads to impairments such as poor postural control, reduced muscle strength and power. Lower limb proprioception, visual contrast sensitivity, hand reaction time, quadriceps strength, and balance [10–12] are also among the most discussed physical attributes associated with falls in older adults. Accumulating evidence broaden the scope by placing strong emphasis on the brain as a key structure for investigation as it plays a critical role in the maintenance of mobility [13–15]. As reviewed in Chaps. 1 and 6, Montero-Odasso and colleagues have postulated that cognition can be a potential target to reduce falls in older adults. From the different cognitive domains, executive functions appear to be of utmost importance in the maintenance of optimal mobility [16–19]. Approximately 60% of older people with cognitive impairment fall annually; this incidence is approximately twice that of cognitively intact peers with further consequences in patients with dementia [10, 20]. Allan and colleagues [21] reported a prevalence of 65.7% for people with dementia to sustain at least one fall over the span of 12 months, and the incidence ratio for falls for the subjects with dementia was significantly higher than that for people without dementia [21]. The cognitively impaired older faller is at increased risk of major injury such as fracture and head trauma [20].

Current evidence suggests that even mild reductions in cognitive abilities are linked with impaired mobility [22–24] and increased falls risk [10, 18, 25, 26]. In a study with over 3400 community-dwelling older adults [24], it was shown slow gait was independently associated with poorer cognitive performance in visual spatial ability, processing speed, attention, and executive functions. In a cross-sectional study, Liu-Ambrose and colleagues [25] demonstrated that older women with mild

cognitive impairment (MCI) demonstrated greater physiological falls risk than older women without MCI. During the last decade, MCI has been associated with higher risk of falls as it is reviewed in Chaps. 6 and 12.

---

## Falls Risk Factors in Older Adults with Cognitive Impairment

Despite the recognition that older adults with cognitive impairment may fall twice as often as their cognitively intact counterparts, there is limited information regarding factors that increase the risk of falls in this population [27]. The increased risk of falls evident in older adults with cognitive impairment may relate to: (1) greater deficits in the risk factors identified in cognitively intact older people; and/or (2) greater number of falls or falls risk factors that are specific to those with cognitive impairment. The first category includes impaired gait and balance which is more common in people with cognitive impairment than in those without it and this may be partially due to central neurodegeneration [28–31]. Wandering and agitation – clinical features specific to cognitive disorders, which are common in dementia, – provide an example of the second category [32–34]. Cognitive impairment may also increase the risk of falls by directly impairing the older person’s judgment when she/he faces environmental challenges such as stepping over an obstacle [35, 36]. Effects due to cognitive impairment may be exacerbated in situations where attention is divided, such as walking while talking [37].

Taylor and colleagues [27] compared performance on physical function and mobility among 138 older adults with cognitive impairment with 276 age- and sex-matched cognitively intact community-dwelling older adults. Older adults with cognitive impairment performed significantly worse than their cognitive intact counterparts in tests of reaction time, grip strength, quadriceps strength, balance in various conditions, functional strength of the lower extremities, and mobility. Notably, older adults with cognitive impairment fell significantly more during a 12-month follow-up observation period than cognitively intact older adults.

Research suggests that limited self-awareness (i.e., denial and underestimation of one’s risk) is an important but understudied falls risk factor that may have particular relevance for older adults with cognitive impairment. Specifically, limited self-awareness of one’s own physical deficits has been identified as a reason why older adults take risks that may lead to falls [38]. Among 91 rehabilitation inpatients, Mihaljcic and colleagues [39] found that different aspects of reduced self-awareness were correlated with being a man, higher educational attainment, neurologic history, lower cognitive ability, and lower functional ability. Robinovitch and coworkers [40] demonstrated that nursing home residents or day care participants with impaired balance tended to overestimate their physical abilities compared with community-dwelling adults. Liu-Ambrose and colleagues [26] compared the accuracy of perceived postural limits between 33 community-dwelling older fallers with good working memory and those with poor working memory. Accuracy of perceived postural limits was assessed by asking participants to first estimate their forward reach capacity and then execute maximum-distance forward reaches.

Older fallers with good working memory demonstrated a significantly lower mean percentage error in perceived reach compared with those with poor working memory. Working memory was independently associated with the percentage error in perceived reach. Results of this study suggest that impaired executive functioning may increase falls risk by impairing older adults' judgment in motor planning for daily activities.

Within the multiple domains of cognition, reduced executive functioning is associated with falls [18, 41–44] and with increased risk of a major fall-related injury [45]. Hausdorff and colleagues [46] found that seniors with a history of falls performed worse on tests of executive functions and attention relative to non-fallers, whereas global cognition scores were not different between the two groups. A systematic review investigated different cognitive domains of cognitive function and their associations with falls or falls risk in adults aged 60 years or older. Of the 25 studies included in the systematic review, 12 reported a significant association between executive functions and falls [47]. Reduced executive functioning is also associated with increased physiological falls risk, such as impaired balance [48, 49], impaired gait [50–53], impaired balance recovery (i.e., reactive postural response) [54], and reduced obstacle avoidance ability (i.e., anticipatory postural response) [35, 55].

Executive functions are higher order cognitive processes that control, integrate, organize, and maintain other cognitive abilities [56]. These cognitive processes include the ability to concentrate, to attend selectively, and to plan and to strategize. Intact executive functioning is also essential to the ability to carry out health-promoting behaviors [28], such as medication management, dietary and lifestyle changes, self-monitoring of responses, and follow-up with health care professionals. Executive functions decline substantially with aging [57] as does the corresponding volume of the frontal-subcortical neuronal systems [50, 56, 58, 59].

There is no unitary executive function – rather, there are distinct processes. Thus, no single measure can adequately measure the construct of executive functions in its entirety. Miyake and coworkers [60] identified three key executive processes that are moderately correlated with one another but each has a distinct purpose. They are: (1) set shifting; (2) updating (or working memory); and (3) selective attention and response inhibition. Set shifting requires one to go back and forth between multiple tasks or mental sets [60]. Updating involves monitoring incoming information for relevance to the task at hand and then appropriately updating the informational content by replacing old, no longer relevant information with new incoming information. Response inhibition involves deliberately inhibiting dominant, automatic, or prepotent responses. In a cross-sectional study, Liu-Ambrose and colleagues [25] found that older women with MCI performed significantly worse on three central executive functions (i.e., set shifting, updating, and selective attention and conflict resolution) compared with counterparts without MCI.

In regard to response inhibition, in a sample of 658 seniors, Anstey et al. [61] found that better accuracy/inhibition performance was associated with reduced falls risk, comparing non-fallers to both single and recurrent fallers. Similarly, Lord and Fitzpatrick [62] reported poorer performance on the Stroop Color Word Test, a

standardized test of selective attention and conflict resolution, in fallers relative to non-fallers. Along the same line, Springer et al. [63] found that those with two or more falls in the past year performed significantly worse than non-fallers on both the Stroop Color Word Test and the Go/No-Go Test – another index of response inhibition. Also, in a prospective study of inpatient falls in an urban rehabilitation hospital, performance on the Stroop Color Word Test predicted falls status beyond that explained by age and functional motor ability [42]. Further evidence of the potential importance of intact response inhibition in falls, using data acquired from a 12-month randomized controlled trial of resistance training in community-dwelling older women, Nagamatsu and colleagues [15] demonstrated that baseline activation levels of brain regions underlying response inhibition (i.e., left frontal orbital cortex extending toward the insula and paracingulate gyrus extending toward the anterior cingulate gyrus) were independently associated with reduced physiological falls risk.

Set shifting has been consistently identified as cognitive falls risk factor. For example, Lord and Fitzpatrick [43] found that fallers performed significantly worse than non-fallers on the Trail Making B Test, a measure of set-shifting ability. McKay and colleagues [64] also demonstrated impaired set shifting, as measured by Trail Making Tests (B-A), was associated with one or more falls in the previous 6 months after controlling for age, sex, overall cognitive function, Parkinson's disease (PD; yes/no), freezing of gait, and PD disease duration. Impaired set shifting was associated with previous falls in older adults with and without PD.

---

## Neural Underpinnings Connecting Falls and Cognitive Impairment

Evidence suggests that impaired mobility, falls, and cognitive impairment are associated and clinically, they are concomitant in older adults [65–68]. Notably, it is important to recognize that the relationship between falls and cognitive impairment is not unidirectional (i.e., impaired cognitive function leads to falls), but rather it is bidirectional [69, 70]. Thus, there is growing recognition that clinical gait abnormalities and falls are early biomarkers of cognitive impairment and dementia. For example, slow gait speed independently predicted decline in cognitive function in older adults [70]. Moreover, a 20-year longitudinal cohort study of 240 older adults found that gait speed decreased a decade prior to the presence of any detectable clinical symptoms of MCI [71]. While the bidirectional relationship between impaired mobility, including falls, and cognitive impairments is recognized, the exact mechanism by which this occurs remains equivocal. Emerging neuroimaging data expands our present understanding in this topic. Under the assumption that mobility and cognitive impairments are both consequence of age-related deteriorations of the brain, it may be postulated that the candidate mechanistic pathway underlying the bidirectional impairments involve alterations in brain structure – for example, white matter lesions; or aberrant brain function – as measured by neural activity or functional connectivity.



## Functional Neural Correlates

Age-related changes in the integrity of the brain can result in alterations in the coordination of functional neural networks that span multiple association cortices [72–74]. As such, functional neuroimaging techniques, such as functional connectivity analysis, have advanced our understanding of the dynamic relationships underlying mobility, falls, and cognition. Functional connectivity analysis examines these disruptions by quantifying the temporal coherence between spatially remote brain regions [75]. Regions with a positive correlation in blood-oxygen-level-dependent signal over time are said to have high functional connectivity, and regions uncorrelated or negatively correlated are thought to be in separate, or possibly competing, brain networks [76].

Aging and neurodegeneration are characterized by disruptions in the coordination of brain networks that support cognitive function and motor control [72, 77–83]. A non-exhaustive list of these networks includes the default mode network (DMN), fronto-executive network (FEN), fronto-parietal network (FPN), and the primary motor sensory network (SMN) [72, 84]. Broadly, the DMN is involved in self-referential thoughts (i.e., accessing and processing of past events for the purpose of problem solving or future planning), memory consolidation, and autobiographical memory [72, 85]. The DMN is active during rest and deactivates during task-oriented processes, to maintain attention and stay on task [86, 87]. The FEN is primarily involved in executive functions, error monitoring of top-down control, and maintaining an extended task-dependent cognitive state [88, 89]. The FPN is primarily involved in attentional control and contributes to cognitive abilities such as response anticipation and conflict processing [89–91]. Optimal brain function may be achieved through incorporating multiple large-scale networks, for instance, the FPN and the SMN are both involved in top-down control of motor planning and execution [81, 92, 93].

Notably, Hsu and colleagues [94] demonstrated that compared with their non-faller counterparts, older adults with a history of multiple falls (i.e.,  $\geq 2$  non-syncopal falls in the previous 12 months) showed aberrant neural network functional connectivity. Specifically, compared with non-fallers, fallers showed more connectivity between the DMN and FPN during simple finger tapping, and significantly less functional connectivity between the FPN and SMN during rest. Moreover, less connectivity between the FPN and SMN during rest was significantly associated with greater decline in both cognitive function and mobility over a 12-month period after accounting for relevant covariates [94]. Hence, a recent history of multiple falls among older adults without a diagnosis of cognitive impairment may indicate sub-clinical changes in brain function and increased risk for subsequent decline.

Crockett and colleagues [95] extended the findings of Hsu and colleagues [94] by examining the relationship of within- as well as between-network connectivity of the DMN with dual-task walking, gait speed, and postural sway in community-dwelling older adult with MCI. They hypothesized that greater functional connectivity within the DMN and between DMN-FPN and DMN-supplementary motor area (SMA) will be associated with poorer performance during dual-task walking,

slower gait speed, and greater postural sway in older adults with MCI. They demonstrated that greater within-DMN connectivity was significantly correlated with poorer dual-task performance. Furthermore, greater internetwork connectivity between the DMN and SMA was significantly correlated with slower gait speed and greater postural sway on the eyes open floor sway task. Thus, greater resting state DMN functional connectivity may be an underlying neural mechanism for reduced dual-task ability, slower gait speed, and greater postural sway, resulting in the increased risk of mobility disability and falling in older adults with MCI.

---

## Falls Prevention in Older Adults with Cognitive Impairment

To date, evidence for falls prevention in older adults with cognitive impairment is inconsistent. No published randomized controlled trials have prevented falls in community-dwelling cognitively impaired older people, and conflicting evidence is reported in hospital and residential care trials [96].

Nevertheless, some evidence suggests exercise and cognitive training may reduce falls risk among older adults with MCI and PD. A systematic review that included 17 randomized controlled trials found that exercise and combined exercise and cognitive training reduced specific falls risk factors, such as gait speed, cognitive function, and balance, in older adults with MCI [97]. Briefly, studies were categorized based on their respective intervention type as physical exercise, cognitive training, and combined exercise and cognitive training. Physical exercise within the context of this systematic review included aerobic exercise, strengthening exercise as well as balance or postural training or a combination of these (i.e., multicomponent exercise). Cognitive training involved both individualized and group-based computer-based cognitive exercises. Combined exercises and cognitive training referred to various combinations of balance and toning exercise (i.e., Tai Chi), resistance training with computerized as well as meditative (i.e., Tai Chi) cognitive training. Of the six included studies on physical exercise, results suggest physical exercise may have positive effect on physical function but variable effect on cognitive function. Multicomponent exercise improved gait (speed and stride length) and showed beneficial effect on global cognitive function and immediate memory recall. Aerobic exercise improved executive functions but not memory. Similarly, different types of cognitive training showed variable cognitive benefits. Broadly, of the eight studies on cognitive training, cognitive training improved executive functions but did not improve global cognitive function; group-based cognitive training showed mixed results (one study reported positive effect and the other reported no effect) on memory, whereas individualized cognitive training did not attain significant effect on memory. Of the three studies included that utilized combined physical and cognitive training, one reported improvement in balance after 1 year of Tai Chi exercise; two studies reported improvements in global cognitive function in addition to better subjective and objective memory (i.e., memory recall) performance. However, neither fall rate nor the number of fallers was reported in any of the studies included. A randomized controlled trial not included in the systematic review examined whether

Tai Chi training can improve cognitive ability and reduce physiological falls risk in older adults with amnesic MCI, a subset of older adults at particular risk for Alzheimer's Disease [98]. The results demonstrated that Tai Chi performed three times per week for 15 weeks significantly improved multiple aspects of cognitive function and moderately reduced physiological falls risk in older adults with amnesic MCI.

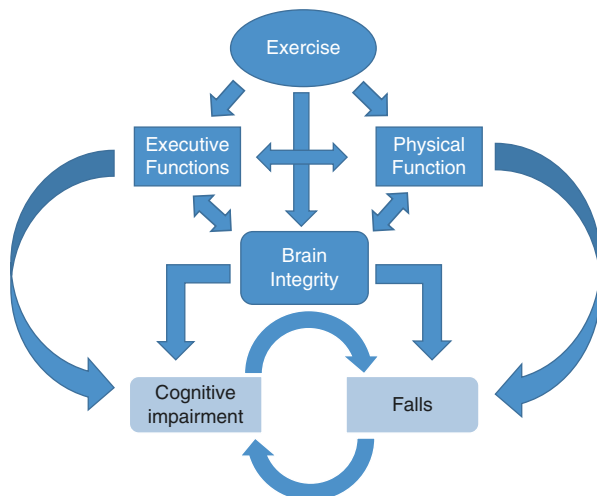
In addition to exercise and cognitive training, proposed strategies to reduce falls include removal of certain medications (i.e., psychotropic drugs) as reviewed in Chaps. 1 and 19 in this book. Medications, particularly benzodiazepines, phenothiazines, and antidepressants, increase the risk of falls via central sedation, orthostatic hypotension, and extrapyramidal side effects. Orthostatic hypotension is implicated in falls caused by medication used to treat dementia and may also be part of autonomic dysfunction in Lewy body dementia [99]. Conversely, there is also growing interest in the use of medications such as myostatin inhibitors, methylphenidate, and acetylcholinesterase inhibitors (i.e., donepezil, galantamine, and rivastigmine) for preventing falls in older adults with cognitive impairment [100].

### Possible Mechanisms Underlying Falls Reduction in Cognitive Impairment

Exercise is a well-established effective falls prevention strategy in community-dwelling older adults [6]. The remaining chapter will summarize existing evidence regarding the possible mechanisms (Fig. 16.1) by which exercise may reduce falls in community-dwelling older adults with MCI.

Of relevance, Liu-Ambrose and colleagues [101] proposed that targeted exercise training may reduce falls by improving cognitive function and introduced the conceptual framework of "Central Benefit Model." The widely accepted dogma is that improved physical function, balance and muscle strength, underlies the

**Fig. 16.1** Conceptual framework of exercise-induced benefits



effectiveness of exercise in reducing falls. However, in a meta-analysis of four OEP randomized trials, falls were significantly reduced by 35% while postural sway significantly improved by only 9% and there was no significant improvement in knee extension strength [102]. These data suggest that improved physical function is one of the many pathways involved in reducing falls risk. Improved cognitive function and associated functional plasticity may be an important yet underappreciated mechanism of how exercise reduces falls in older adults. This concept challenges the current paradigm of falls prevention strategies that focus solely on improving physical function and minimizing environmental hazards and highlights the potential impact of exercised on CNS function.

The Central Benefit Model highlights that reduced executive functions may increase the propensity to fall via various pathways including impaired balance [48] and gait [51], reduced attentional capacity, impaired central processing and integration, and impaired execution of postural responses. Reduced executive functions may also increase falls risk via decreased judgment and diminished self-regulation [42], or indirectly increase falls risk via secondary disruptions in executive-related behavior, such as a loss in motivation and initiation [103]. Impaired balance and gait and loss of motivation and initiation may also lead to further reductions in executive functions (i.e., feedback loop). Notably, targeted exercise training reduces falls risk in older adults by maintaining or promoting executive functions.

Evidence from randomized controlled trials supports the Central Benefit Model's central hypothesis that exercise may reduce falls by improved executive functions. A proof-of-concept randomized controlled trial provided evidence to suggest that the OEP significantly reduced falls by 47% among older adults aged 70 years and older who sought medical attention due to a fall – in the absence of significant improvement in physical function (i.e., balance and muscle strength) [104]. Notably, cognitive performance of selective attention and conflict resolution improved in the OEP group as compared with the usual care (i.e., control) group. Another 12-month randomized controlled trial demonstrated that improved selective attention and conflict resolution secondary to 12 months of progressive resistance training was associated with improved usual gait speed [105] – a significant and independent predictor of falls and fracture risk in older women [106].

The same randomized controlled trial also provided insight into the underlying common neural mechanism by which progressive resistance training promotes executive functions and gait speed. In a subset of participants who underwent MRI scanning, participants who received progressive resistance training twice per week had reduced white matter lesion progression compared with those in the active control (i.e., balance and tone exercises) [107]. Reduced white matter lesion progression was significantly associated with change in usual gait speed ( $r = -0.31$ ,  $p = 0.049$ ) with a similar correlation with change in executive functions that did not reach statistical significance ( $r = 0.30$ ;  $p = 0.06$ ). Aligning with this evidence, a recent systematic review suggests physical training may promote myelin sheath – the primary constituent of brain white matter – regeneration [108]. The 13 studies included in this review consisted of animal research focused on rats with an intervention periods ranging from 14 to 70 days. Within the 13 articles, beneficial effects were reported from low and moderate intensity endurance exercise as well as low and moderate intensity

treadmill training and swimming. Despite no translational work having been completed in human older adults, these results provide promising insight into physical exercise-induced white matter regeneration, which may ameliorate physical and cognitive function decline secondary to demyelination.

Using functional MRI data from a 6-month single-blinded randomized controlled trial in older adults with MCI due to small vessel disease, Hsu and colleagues [109] demonstrated that progressive aerobic exercise of moderate intensity may promote mobility by maintaining the integrity of the FPN connectivity. Specifically, reduced FPN connectivity from baseline to trial completion correlated with improved Timed-Up and Go Test performance. Diminished connectivity may represent greater efficiency as the networks can more effectively allocate resources to areas of immediate importance. Certainly, emerging evidence suggests that lifestyle interventions can improve neural efficiency [110, 111]. Additional future research is needed and welcomed to assess the validity of the proposed Central Benefit Model [101].

---

## Summary

Given the association between impaired cognitive function – particularly impaired executive functions – and falls, as well as increased falls risk, future falls risk screening needs to place more emphasis on the assessment of specific cognitive processes, including selective attention/conflict resolution and dual-tasking. In regard to future falls prevention programs, health care providers should consider implementing interventions that consist of components that specifically target executive functions. For example, both aerobic exercise and progressive resistance training offer benefits in improving neural plasticity in regions and structures involved in executive functions [112, 113]. As such, both exercise regimens should be integrated into the current exercise-based falls prevention strategies on balance training.

Future research studies will also be needed to help us advance our understanding, in which multimodal neural imaging techniques (i.e., simultaneous imaging acquisition of electroencephalography/functional MRI or integrated imaging protocol including structural MRI, diffusion tensor MRI, functional MRI, etc.) as well as multimodal intervention programs that implement both exercise and cognitive training can help us more accurately characterize the mechanistic pathways underlying exercise, cognitive function, and mobility. Knowledge gained will facilitate the development of efficacious falls prevention interventions for older adults with cognitive impairment.

---

## References

1. Satariano WA, Guralnik JM, Jackson RJ, Marottoli RA, Phelan EA, Prohaska TR. Mobility and aging: new directions for public health action. *Am J Public Health*. 2012;102(8):1508–15.
2. Rosano C, Newman AB, Katz R, Hirsch CH, Kuller LH. Association between lower digit symbol substitution test score and slower gait and greater risk of mortality and of developing incident disability in well-functioning older adults. *J Am Geriatr Soc*. 2008;56(9):1618–25.

3. Odenheimer G, Funkenstein HH, Beckett L, Chown M, Pilgrim D, Evans D, et al. Comparison of neurologic changes in 'successfully aging' persons vs the total aging population. *Arch Neurol*. 1994;51(6):573–80.
4. Centers for Disease Control and Prevention. Prevalence and most common causes of disability among adults—United States, 2005. *MMWR Morb Mortal Wkly Rep*. 2009;58(16):421–6.
5. Rich N. Levels of evidence. *J Women's Health Phys Therap*. 2005;29:19–20.
6. Gillespie LD, Robertson MC, Gillespie WJ, Lamb SE, Gates S, Cumming RG, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2009;2:CD007146.
7. Sherrington C, Michaleff ZA, Fairhall N, Paul SS, Tiedemann A, Whitney J, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. *Br J Sports Med*. 2017;51(24):1750–8.
8. Davis JC, Robertson MC, Ashe MC, Liu-Ambrose T, Khan KM, Marra CA. Does a home based strength and balance programme in people aged  $\geq 80$  years provide the best value for money to prevent falls?: a systematic review of economic analyses of falls prevention interventions. *Br J Sports Med*. 2009;44(2):80–9.
9. Rantakokko M, Manty M, Rantanen T. Mobility decline in old age. *Exerc Sport Sci Rev*. 2013;41(1):19–25.
10. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319(26):1701–7.
11. Lord SR, Clark RD, Webster IW. Physiological factors associated with falls in an elderly population. *J Am Geriatr Soc*. 1991;39(12):1194–200.
12. Lord SR, Ward JA, Williams P, Anstey KJ. Physiological factors associated with falls in older community-dwelling women. *J Am Geriatr Soc*. 1994;42(10):1110–7.
13. Rosano C, Aizenstein HJ, Studenski S, Newman AB. A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2007a;62(9):1048–55.
14. Rosano C, Brach J, Studenski S, Longstreth WT Jr, Newman AB. Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. *Neuroepidemiology*. 2007b;29(3–4):193–200.
15. Nagamatsu LS, Hsu CL, Handy TC, Liu-Ambrose T. Functional neural correlates of reduced physiological falls risk. *Behav Brain Funct*. 2011;7:37.
16. Hsu CL, Nagamatsu LS, Davis JC, Liu-Ambrose T. Examining the relationship between specific cognitive processes and falls risk in older adults: a systematic review. *Osteoporos Int*. 2012a;23:2409.
17. Rapport LJ, Hanks RA, Millis SR, Deshpande SA. Executive functioning and predictors of falls in the rehabilitation setting. *Arch Phys Med Rehabil*. 1998a;79(6):629–33.
18. Anstey KJ, von Sanden C, Luszcz MA. An 8-year prospective study of the relationship between cognitive performance and falling in very old adults. *J Am Geriatr Soc*. 2006;54(8):1169–76.
19. American Geriatrics Society. Guideline for the prevention of falls in older persons. *J Am Geriatr Soc*. 2001;49:664–72.
20. van Dijk PT, Meulenbergh OG, van de Sande HJ, Habbema JD. Falls in dementia patients. *Gerontologist*. 1993;33(2):200–4.
21. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. *PLoS One*. 2009;4(5):e5521.
22. Doi T, Shimada H, Makizako H, Tsutsumimoto K, Hotta R, Nakakubo S, et al. Mild cognitive impairment, slow gait, and risk of disability: a prospective study. *J Am Med Dir Assoc*. 2015a;16(12):1082–6.
23. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, et al. Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc*. 2008;56(7):1244–51.
24. Doi T, Shimada H, Park H, Makizako H, Tsutsumimoto K, Uemura K, et al. Cognitive function and falling among older adults with mild cognitive impairment and slow gait. *Geriatr Gerontol Int*. 2015b;15(8):1073–8.



25. Liu-Ambrose TY, Ashe MC, Graf P, Beattie BL, Khan KM. Increased risk of falling in older community-dwelling women with mild cognitive impairment. *Phys Ther*. 2008a;88(12):1482–91.
26. Liu-Ambrose T, Ahamed Y, Graf P, Feldman F, Robinovitch SN. Older fallers with poor working memory overestimate their postural limits. *Arch Phys Med Rehabil*. 2008b;89(7):1335–40.
27. Taylor ME, Delbaere K, Lord SR, Mikolaizak AS, Close JCT. Physical impairments in cognitively impaired older people: implications for risk of falls. *Int Psychogeriatr*. 2012;25(1):148–56.
28. Kuo HK, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci*. 2004a;59(8):818–26.
29. Kerber KA, Enrietto JA, Jacobson KM, Baloh RW. Disequilibrium in older people: a prospective study. *Neurology*. 1998;51(2):574–80.
30. Starr JM, Leaper SA, Murray AD, Lemmon HA, Staff RT, Deary IJ, et al. Brain white matter lesions detected by magnetic resonance imaging are associated with balance and gait speed. *J Neurol Neurosurg Psychiatry*. 2003;74(1):94–8. <https://doi.org/10.1136/jnnp.74.1.94>.
31. Wolfson L. Gait and balance dysfunction: a model of the interaction of age and disease. *Neuroscientist*. 2001;7(2):178–83.
32. Marx MS, Cohen-Mansfield J, Werner P. Agitation and falls in institutionalized elderly persons. *J Appl Gerontol*. 1990;9(1):106–17.
33. Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. *JAMA*. 1987;257(11):1492–5.
34. McConnell EA. Managing patient falls and wandering. *Nurs Manag*. 1998;29(8):75.
35. Di Fabio RP, Kurszewski WM, Jorgenson EE, Kunz RC. Footlift asymmetry during obstacle avoidance in high-risk elderly. *J Am Geriatr Soc*. 2004;52(12):2088–93.
36. Di Fabio RP, Zampieri C, Henke J, Olson K, Rickheim D, Russell M. Influence of elderly executive cognitive function on attention in the lower visual field during step initiation. *Gerontology*. 2005;51(2):94–107.
37. Liu-Ambrose T, Katarynych LA, Ashe MC, Nagamatsu LS, Hsu CL. Dual-task gait performance among community-dwelling senior women: the role of balance confidence and executive functions. *J Gerontol A Biol Sci Med Sci*. 2009;64(9):975–82.
38. Mihaljcic T, Haines TP, Ponsford JL, Stolwyk RJ. Development of a new self-awareness of falls risk measure (SAFRM). *Arch Gerontol Geriatr*. 2014;59(2):249–56.
39. Mihaljcic T, Haines TP, Ponsford JL, Stolwyk RJ. Self-awareness of falls risk among elderly patients: characterizing awareness deficits and exploring associated factors. *Arch Phys Med Rehabil*. 2015;96(12):2145–52.
40. Robinovitch SN, Cronin T. Perception of postural limits in elderly nursing home and day care participants. *J Gerontol A Biol Sci Med Sci*. 1999;54(3):B124–30; discussion B31.
41. Rapport LJ, Webster JS, Flemming KL, Lindberg JW, Godlewski MC, Brees JE, et al. Predictors of falls among right-hemisphere stroke patients in the rehabilitation setting. *Arch Phys Med Rehabil*. 1993;74(6):621–6.
42. Rapport LJ, Hanks RA, Millis SR, Deshpande SA. Executive functioning and predictors of falls in the rehabilitation setting. *Arch Phys Med Rehabil*. 1998b;79(6):629–33.
43. Lord S, Fitzpatrick R. Choice stepping reaction time: a composite measure of fall risk in older people. *J Gerontol*. 2001a;10:M627–32.
44. Lundin-Olsson L, Nyberg L, Gustafson Y. “Stops walking when talking” as a predictor of falls in elderly people. *Lancet*. 1997;349(9052):617.
45. Nevitt MC, Cummings SR, Hudes ES. Risk factors for injurious falls: a prospective study. *J Gerontol*. 1991;46(5):M164–70.
46. Hausdorff JM, Doniger GM, Springer S, Yogev G, Simon ES, Giladi N. A common cognitive profile in elderly fallers and in patients with Parkinson’s disease: the prominence of impaired executive function and attention. *Exp Aging Res*. 2006;32(4):411–29.
47. Hsu CL, Nagamatsu LS, Davis JC, Liu-Ambrose T. Examining the relationship between specific cognitive processes and falls risk in older adults: a systematic review. *Osteoporos Int*. 2012b;23(10):2409–24.
48. Dault MC, Geurts AC, Mulder TW, Duysens J. Postural control and cognitive task performance in healthy participants while balancing on different support-surface configurations. *Gait Posture*. 2001;14(3):248–55.



49. Maki BE, Zecevic A, Bateni H, Kirshenbaum N, McIlroy WE. Cognitive demands of executing postural reactions: does aging impede attention switching? *Neuroreport*. 2001;12(16):3583–7.
50. Kuo H-K, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci*. 2004b;59(8):M818–26.
51. Holtzer R, Verghese J, Xue X, Lipton RB. Cognitive processes related to gait velocity: results from the Einstein Aging Study. *Neuropsychology*. 2006;20(2):215–23.
52. Ble A, Volpato S, Zuliani G, Guralnik JM, Bandinelli S, Lauretani F, et al. Executive function correlates with walking speed in older persons: the InCHIANTI study. *J Am Geriatr Soc*. 2005;53(3):410–5.
53. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord*. 2006a;21:950.
54. Brauer SG, Woollacott M, Shumway-Cook A. The interacting effects of cognitive demand and recovery of postural stability in balance-impaired elderly persons. *J Gerontol A Biol Sci Med Sci*. 2001;56(8):M489–96.
55. Persad CC, Giordani B, Chen HC, Ashton-Miller JA, Alexander NB, Wilson CS, et al. Neuropsychological predictors of complex obstacle avoidance in healthy older adults. *J Gerontol B Psychol Sci Soc Sci*. 1995;50(5):P272–7.
56. Stuss DT, Alexander MP. Executive functions and the frontal lobes: a conceptual view. *Psychol Res*. 2000;63(3–4):289–98.
57. West RL. An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull*. 1996;120(2):272–92.
58. Cummings JL. Frontal-subcortical circuits and human behavior. *Arch Neurol*. 1993;50(8):873–80.
59. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330(25):1769–75.
60. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cognit Psychol*. 2000;41(1):49–100.
61. Anstey KJ, Wood J, Kerr G, Caldwell H, Lord SR. Different cognitive profiles for single compared with recurrent fallers without dementia. *Neuropsychology*. 2009;23(4):500–8.
62. Lord SR, Fitzpatrick RC. Choice stepping reaction time: a composite measure of falls risk in older people. *J Gerontol A Biol Sci Med Sci*. 2001b;56(10):M627–32.
63. Springer S, Giladi N, Peretz C, Yogev G, Simon ES, Hausdorff JM. Dual-tasking effects on gait variability: the role of aging, falls, and executive function. *Mov Disord*. 2006b;21(7):950–7.
64. McKay JL, Lang KC, Ting LH, Hackney ME. Impaired set shifting is associated with previous falls in individuals with and without Parkinson's disease. *Gait Posture*. 2018;62:220–6.
65. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60(11):2127–36.
66. Verghese J, Holtzer R, Lipton RB, Wang C. Quantitative gait markers and incident fall risk in older adults. *J Gerontol A Biol Sci Med Sci*. 2009;64(8):896–901.
67. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buschke H. Abnormality of gait as a predictor of non-Alzheimer's dementia. *N Engl J Med*. 2002;347(22):1761–8.
68. Verghese J, Wang C, Allali G, Holtzer R, Ayers E. Modifiable risk factors for new-onset slow gait in older adults. *J Am Med Dir Assoc*. 2016;17(5):421–5.
69. Atkinson HH, Rosano C, Simonsick EM, Williamson JD, Davis C, Ambrosius WT, et al. Cognitive function, gait speed decline, and comorbidities: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci*. 2007;62(8):844–50.
70. Inzitari M, Newman AB, Yaffe K, Boudreau R, de Rekeneire N, Shorr R, et al. Gait speed predicts decline in attention and psychomotor speed in older adults: the health aging and body composition study. *Neuroepidemiology*. 2007;29(3–4):156–62.
71. Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J. The trajectory of gait speed preceding mild cognitive impairment. *Arch Neurol*. 2010;67(8):980–6.

72. Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, et al. Disruption of large-scale brain systems in advanced aging. *Neuron*. 2007;56(5):924–35.
73. Colcombe SJ, Kramer AF, Erickson KI, Scalf P. The implications of cortical recruitment and brain morphology for individual differences in inhibitory function in aging humans. *Psychol Aging*. 2005;20(3):363–75.
74. Marquez de la Plata CD, Garcés J, Shokri Kojori E, Grinnan J, Krishnan K, Pidikiti R, et al. Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Arch Neurol*. 2011;68(1):74–84.
75. Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Functional connectivity: the principal-component analysis of large (PET) data sets. *J Cereb Blood Flow Metab*. 1993;13(1):5–14.
76. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A*. 2005;102(27):9673–8.
77. Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. *Curr Opin Neurobiol*. 2005;15(2):245–51.
78. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol*. 2009;60:173–96.
79. Persson J, Nyberg L, Lind J, Larsson A, Nilsson LG, Ingvar M, et al. Structure-function correlates of cognitive decline in aging. *Cereb Cortex*. 2006;16(7):907–15.
80. Vidoni ED, Thomas GP, Honea RA, Loskutova N, Burns JM. Evidence of altered corticomotor system connectivity in early-stage Alzheimer's disease. *J Neurol Phys Ther*. 2012;36(1):8–16.
81. Wu T, Wang L, Chen Y, Zhao C, Li K, Chan P. Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. *Neurosci Lett*. 2009;460(1):6–10.
82. Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. *Curr Opin Neurol*. 2008;21(4):424–30.
83. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A*. 2004;101(13):4637–42.
84. Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, et al. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. *Front Aging Neurosci*. 2010;2:32.
85. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann NY Acad Sci*. 2008;1124:1–38.
86. Raichle ME. The brain's default mode network. *Annu Rev Neurosci*. 2015;38:433–47.
87. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001;98(2):676–82.
88. Dosenbach NU, Visscher KM, Palmer ED, Miezin FM, Wenger KK, Kang HC, et al. A core system for the implementation of task sets. *Neuron*. 2006;50(5):799–812.
89. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci*. 2007;27(9):2349–56.
90. Fogassi L, Luppino G. Motor functions of the parietal lobe. *Curr Opin Neurobiol*. 2005;15(6):626–31.
91. Sridharan D, Levitin DJ, Menon V. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A*. 2008;105(34):12569–74.
92. Wise SP, Boussaoud D, Johnson PB, Caminiti R. Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annu Rev Neurosci*. 1997;20:25–42.
93. Wymbs NF, Bassett DS, Mucha PJ, Porter MA, Grafton ST. Differential recruitment of the sensorimotor putamen and frontoparietal cortex during motor chunking in humans. *Neuron*. 2012;74(5):936–46.
94. Hsu CL, Voss MW, Handy TC, Davis JC, Nagamatsu LS, Chan A, et al. Disruptions in brain networks of older fallers are associated with subsequent cognitive decline: a 12-month prospective exploratory study. *PLoS One*. 2014;9(4):e93673.

95. Crockett RA, Hsu CL, Best JR, Liu-Ambrose T. Resting state default mode network connectivity, dual task performance, gait speed, and postural sway in older adults with mild cognitive impairment. *Front Aging Neurosci.* 2017;9:423.
96. Close JC, Wesson J, Sherrington C, Hill KD, Kurrle S, Lord SR, et al. Can a tailored exercise and home hazard reduction program reduce the rate of falls in community dwelling older people with cognitive impairment: protocol paper for the i-FOCIS randomised controlled trial. *BMC Geriatr.* 2014;14:89.
97. Lipardo DS, Aseron AMC, Kwan MM, Tsang WW. Effect of exercise and cognitive training on falls and fall-related factors in older adults with mild cognitive impairment: a systematic review. *Arch Phys Med Rehabil.* 2017;98(10):2079–96.
98. Sungkarat S, Boripuntakul S, Chattipakorn N, Watcharasaksilp K, Lord SR. Effects of Tai Chi on cognition and fall risk in older adults with mild cognitive impairment: a randomized controlled trial. *J Am Geriatr Soc.* 2017;65(4):721–7.
99. Shaw FE, Kenny RA. Can falls in patients with dementia be prevented? *Age Ageing.* 1998;27(1):7–9.
100. Lord SR, Close JCT. New horizons in fall prevention. *Age Ageing.* 2018;47:492.
101. Liu-Ambrose T, Nagamatsu LS, Hsu CL, Bolandzadeh N. Emerging concept: ‘central benefit model’ of exercise in falls prevention. *Br J Sports Med.* 2013;47(13):856.
102. Robertson MC, Campbell AJ, Gardner MM, Devlin N. Preventing injuries in older people by preventing falls: a meta-analysis of individual-level data. *J Am Geriatr Soc.* 2002;50(5):905–11.
103. Ylikoski R, Hanninen T. Assessment of executive function in clinical trials. *Int Psychogeriatr.* 2003;15(Suppl 1):219–24.
104. Liu-Ambrose T, Donaldson MG, Ahamed Y, Graf P, Cook WL, Close J, et al. Otago home-based strength and balance retraining improves executive functioning in older fallers: a randomized controlled trial. *J Am Geriatr Soc.* 2008c;56(10):1821–30.
105. Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance training and executive functions: a 12-month randomized controlled trial. *Arch Intern Med.* 2010;170(2):170–8.
106. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott A, Hausherr E, et al. Fall-related factors and risk of hip fracture: The EPIDOS prospective study. *Lancet.* 1996;348:145–9.
107. Bolandzadeh N, Tam R, Handy TC, Nagamatsu LS, Hsu CL, Davis JC, et al. Resistance training and white matter lesion progression in older women: exploratory analysis of a 12-month randomized controlled trial. *J Am Geriatr Soc.* 2015;63(10):2052–60.
108. Feter N, Freitas M, Gonzales N, Umpierre D, Cardoso RK, Rombaldi A. Effects of physical exercise on myelin sheath regeneration: a systematic review and meta-analysis. *Sci Sports.* 2018;33(1):8–21.
109. Hsu CL, Best JR, Wang S, Voss MW, Hsiung RGY, Munkacsy M, et al. The impact of aerobic exercise on fronto-parietal network connectivity and its relation to mobility: an exploratory analysis of a 6-month randomized controlled trial. *Front Hum Neurosci.* 2017;11:344.
110. Smith JC, Nielson KA, Antuono P, Lyons JA, Hanson RJ, Butts AM, et al. Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. *J Alzheimers Dis.* 2013;37(1):197–215.
111. Nishiguchi S, Yamada M, Tanigawa T, Sekiyama K, Kawagoe T, Suzuki M, et al. A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: a randomized controlled trial. *J Am Geriatr Soc.* 2015;63(7):1355–63.
112. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A.* 2004;101(9):3316–21.
113. Liu-Ambrose T, Nagamatsu LS, Voss MW, Khan KM, Handy TC. Resistance training and functional plasticity of the aging brain: a 12-month randomized controlled trial. *Neurobiol Aging.* 2012;33(8):1690–8.



# Cognitive Training and Mobility: Implications for Falls Prevention

# 17

Karen Z. H. Li and L. Bherer

Over the past two decades, accumulating evidence indicates that cognitive capacity becomes increasingly implicated in postural stability with healthy aging, as signaled by several scholarly reviews [1–3], as well as many of the chapters in this volume. In this chapter, we first consider the assumptions underlying the general strategy of strengthening cognitive capacity to improve mobility by reviewing the evidence of cognitive involvement in gait and posture in old age. We next discuss the extant literature on cognitive training, with special consideration of specificity of training, transfer effects, and neural plasticity in aging. We then review the growing literature on cognitive training and its impact on gait, balance, and falls.

---

K. Z. H. Li (✉)

Department of Psychology, Concordia University, Montreal, QC, Canada

Centre for Research in Human Development, Concordia University, Montreal, QC, Canada

PERFORM Centre, Concordia University, Montreal, QC, Canada

e-mail: [karen.li@concordia.ca](mailto:karen.li@concordia.ca)

L. Bherer

PERFORM Centre, Concordia University, Montreal, QC, Canada

Department of Medicine, Université de Montréal, Montreal, QC, Canada

Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal,  
Montreal, QC, Canada

Research Center, Montreal Heart Institute, Montreal, QC, Canada

e-mail: [louis.bherer@umontreal.ca](mailto:louis.bherer@umontreal.ca)

© Springer Nature Switzerland AG 2020

M. Montero-Odasso, R. Camicioli (eds.), *Falls and Cognition in Older Persons*,  
[https://doi.org/10.1007/978-3-030-24233-6\\_17](https://doi.org/10.1007/978-3-030-24233-6_17)

289

## Why Use Cognitive Training to Address Mobility and Falls to Begin with?

The rationale for using cognitive training to improve mobility and reduce falls in aging rests on the evidence for an increased recruitment of brain regions that subserve both cognitive abilities and postural control. Empirical evidence for the involvement of cognitive processes and neural circuits during gait and balance tasks comes from observational or correlational studies linking measures of mobility (e.g., usual gait speed) and measures of cognitive functioning, experimental studies using dual-task methodology (e.g., assessment of walking paired with a concurrent cognitive task), and functional neuroimaging studies of gait and balance.

**Correlational Evidence** Seminal evidence for the link between sensory–sensorimotor and cognitive performances comes from the lifespan developmental Berlin Aging Study (BASE), in which a representative sample of older adults aged 70 and over were assessed on their sensory (vision, hearing), motor (gait speed, balance), and cognitive functioning (memory, attention, speed) [4, 5]. Based upon this strong connection between sensory motor and cognitive functioning, researchers postulated a single factor, or common cause, to account for the substantial shared variance among functional domains in old age, exploring central age-related factors such as neurotransmitter depletion and neural noise [6]. Subsequent examinations of this common cause hypothesis led others to suggest a compensatory allocation of cognitive or attentional resources in old age to counteract age-related declines in sensory or motor functions [7–9]. More direct correlational examinations of gait reveal associations between executive functions such as response inhibition (measured by the Stroop interference task) or verbal fluency with gait parameters such as stride time variability and gait velocity [10–12]. In addition to cross-sectional studies, others have shown that slow gait predicts mild cognitive impairment [13], non-Alzheimer’s dementia [14], Alzheimer’s, vascular, and Lewy body type dementias [15], and future cognitive decline [16, 17]. Structural neuroimaging evidence of gray matter volumes and white matter integrity provide converging evidence for the behavioral observational studies [18]. For example, reductions in usual gait speed are associated with decreased gray matter volume in the hippocampus [19], which plays a central role in learning and memory. Using diffusion tensor imaging, white matter integrity, indexed by functional anisotropy, indicates similar associations between putative brain regions that support high-level cognitive control (e.g., anterior corpus callosum) and usual gait speed [20]. More recently, Allali et al. [21] reported that brain networks associated with gait control vary according to walking speed and depend on walking conditions (i.e., normal walking, rapid walking, and dual-task condition) and suggested that gait control in aging involved a distributed network including regions for emotional control that are recruited in challenging walking conditions. Together, these off-line techniques implicate common neural structures associated with cognitive control functions such as inhibition, coordination, and dividing attention as well as different aspects of gait.

**Experimental Dual-Task Evidence** A more direct examination of the involvement of cognition in gait comes from dual-task designs, in which motor performance is assessed under full attention (single-task) and divided attention (dual-task) conditions [2, 22]. The role of dual-task interference on gait and falls and in falls risk assessment is addressed in Chap. 6. Numerous demonstrations of reduced gait velocity, increased gait variability, and increased postural instability as a function of cognitive load provide evidence that these performance decrements, or dual-task costs, are due to competition for common cognitive capacity or neural structures, and that such costs are exacerbated oftentimes by cognitive impairment and postural threat [3, 23]. Recent developments in functional neuroimaging techniques, as reviewed in this volume and elsewhere [18], further corroborate the recruitment of cognitive attentional capacity during gait and balance [18, 24, 25]. For example, using functional near-infrared spectroscopy (fNIRS), Fraser et al. [26] recently showed increased blood flow (HBO<sub>2</sub> and HBR) in dorsolateral and ventrolateral PFC during walking with increased bilaterality in older adults' dual-task gait. Notably, these same brain regions are also associated with working memory, attention, motor inhibition, and motor planning [23]. Using more temporally sensitive electroencephalography (EEG), recent spectral power analyses have revealed that the gamma frequency band (30–80 Hz) is sensitive to manipulations of attentional load during walking, in older adults and in neurological patients. More gamma band activity was observed in neurological patients than in healthy older adults [27], providing convergent evidence for cognitive compensation.

Importantly, the relationship between dual-task costs and degree of cognitive load appears to be curvilinear in a “U” shape, with very simple cognitive tasks causing dual-task facilitation (i.e., improved postural stability or gait) as compared to single-task motor performance, but growing dual-task costs as cognitive load becomes more challenging [28–30]. The facilitative effect of a mild cognitive load is possibly due to heightened arousal that increased demands create, without nearing the limit of cognitive capacity. Alternatively, performance of balance or gait tasks under full attention might create an unnatural focus of attention on the normally automatic task that compromises motor performance [28]. A second important trend in this area is the concept of attentional allocation favoring postural control, termed the posture-first principle [31], expressed in dual-task designs as finding smaller dual-task costs in the motor domain and larger costs in cognitive performance. Older adults have shown a greater tendency to exhibit this posture first pattern as compared to young adults, who exhibit a more even allocation of attention [32].

Together, the behavioral and neuroimaging evidence points to the recruitment of prefrontal brain regions that support both motor functioning and high-level executive functions. Normative age-related reductions in prefrontal gray and white matter [33] suggest that the recruitment of such neural structures during balancing or walking may reach performance limitations more quickly despite the increased need to compensate for aging motor systems. Therefore, strengthening the efficiency of prefrontal regions may enhance compensatory capacity and thereby improve postural control, gait, and reduce the risk of falling in older adults.



## Cognitive Training in Aging

**Cognitive Training** Over the past two decades, numerous studies have shown that cognitive training improves cognitive performances in older adults, showing maintained cognitive plasticity in older age [34–37]. In the last year, cognitive stimulation and training have been recognized as key interventions and recommendations to prevent cognitive decline and dementia [38, 39]. Cognitive training entails specifically designed programs targeting specific aspects of cognition and usually involves individualized feedback to improve performance on a given task. Many studies have shown that performances in various cognitive domains can be improved following cognitive training: working memory, episodic memory [40], speed of processing and reasoning [41], divided attention abilities, and dual-tasking [34, 42–44]. In the context of our chapter that targets gait and mobility, this section will focus specifically on dual-task and working memory training.

Kramer and collaborators conducted one of the first dual-task training studies in older adults [42, 43]. They used an adaptive and individualized computerized training program in which participants performed a monitoring task (e.g., resetting a moving gauge when it reached a critical point) combined with an alphabet–arithmetic task (e.g., solve  $K - 3 = ?$ ). They showed that training substantially enhanced performance in both younger and older adults. More specifically, both younger and older adults learned to effectively coordinate the two tasks, but older adults also showed greater training benefits than younger adults. Furthermore, the skills learned during training transferred to a novel dual-task situation and these benefits were retained for up to 2 months (45–60 days).

Using a similar approach, Bherer et al. [34] conducted a set of studies in which the dual-task paradigm involved performing two reaction time tasks. Participants were trained on two discrimination tasks performed alone and concurrently: a visual and an auditory discrimination task with responses provided manually. Results showed that training induced age-equivalent improvements and that training gains transferred to tasks with different stimuli on the ability to maintain multiple task sets and the ability to coordinate multiple concurrent tasks. In another study [35], young and old adults were trained on two visual discrimination tasks both requiring motor responses. Here again, older adults showed improvements similar to younger adults following dual-task training, and improved even more than young adults for accuracy, providing further evidence of cognitive plasticity for executive control processes in aging.

As for working memory training, several studies have shown its beneficial effects in older adults. For instance, Brehmer and collaborators [45] trained younger and older adults on visual and verbal working memory for 5 weeks using COGMED with an adaptive training and compared them to a low activity control group. The authors observed that training gains were somewhat greater for younger than for older adults in some tasks, yet comparable in both age groups in other tasks. In another study, Zinke and colleagues [46] trained older adults on verbal and visuospatial working memory, as well as executive control, and compared them to a



control group. They observed that participants having followed the training showed significant gains compared to controls on the three trained tasks. Interestingly, when investigating predictors of training gains, they found that older age predicted smaller training gains, whereas lower baseline working memory performances predicted higher gains. Finally, a recent meta-analysis by Karbach and Verhaeghen [47] found that working memory and executive function process-based cognitive trainings lead to significant and large gains on the trained task in older adults.

**Cognitive Training and Transfer to Untrained Tasks** An important issue rising from these studies is whether or not cognitive training, and more precisely dual-task and executive control training, can improve untrained tasks. Lussier et al. [44] examined the extent to which training gains transferred to untrained tasks. Older and younger adults took part in dual-task training involving two visual discrimination tasks with manual responses on the keyboard and were compared to controls. Participants also completed three transfer tasks where either stimulus modality (auditory) or response modality (wheel and pedal) or both were changed (auditory and wheel and pedal responses). It was first found that the training group showed larger improvements than the control group on all three transfer tasks. Indeed, training improved participants' ability to coordinate responses, but only in conditions involving either new stimuli or response modalities, but not both. Interestingly, transfer effects were similar among older and younger adults. Using an extended version of the same dual-task paradigm, Lussier et al. [48] compared two dual-task training conditions, one in which the training context varies between sessions (heterogeneous training) and the other in a fixed training context (homogeneous training) to an active control group (taking computer lessons for the same number of sessions than training). The authors reported that heterogeneous and homogeneous training led to larger near-modality transfer effects than the active placebo (computer lessons). Transfer effects were roughly comparable in both training groups, but heterogeneous training led to a steeper improvement of the dual-task coordination learning curve within training sessions. They concluded that heterogeneous training showed modest advantages over homogeneous training. Another ingredient of a more efficient dual-task training protocol to achieve larger transferable gains is to vary attention priority among tasks, the so-called variable priority training (VPT). Past studies have shown the advantage of VPT compared to fixed priority training (FPT) [42]. In a recent study, Lussier et al. [49] compared transfer effects induced by VPT and FPT in healthy older adults. VPT and FPT subjects were trained on a complex dual-task condition with variable stimulus timings in order to promote more flexible and self-guided strategies with regard to attentional priority devoted to the concurrent tasks. Real-time individualized feedback was provided to encourage improvement. Both groups were also compared to an active placebo group that attended computer classes. Near- and far-modality transfer tasks were used to assess the generalization of transfer effects. Results showed that while both VPT and FPT showed near-modality transfer effects, VPT induced significantly larger transfer effects than FPT. However, and more interestingly, evidence for larger transfer effects in VPT than FPT on a far-modality transfer task was also observed and only

the VPT group showed an increased ability to coordinate two concurrent tasks, as indexed by a reduced dual-task cost. Together, these studies provide valuable insights on benefits arising from variability in the training protocol and in priority instruction for maximizing transfer effects.

Transfer effects following working memory training have also been investigated. For instance, Brehmer and collaborators [45] found larger near-transfer effects in younger adults than in older adults following a 5-week working memory training on one task (Span Board task), and comparable transfer effects between both age groups on another near-transfer task (Digit Span Forward and Backward). Moreover, similar magnitudes of far-transfer effects were observed in both groups following training (Paced Auditory Serial Addition Test). Finally, training and transfer gains were maintained at the 3-month follow-up. In the study by Zinke et al. [46], older adults trained on verbal and visuospatial working memory showed near-transfer effects on a verbal working memory task, and far-transfer effects on a fluid intelligence task (Raven's progressive matrices). Moreover, the transfer effects were still present at the 9-month follow-up. Finally, in their meta-analysis, Karbach and Verhaeghen [47] found that working memory and executive function trainings result in significant and rather large transfer effects to near-transfer tasks that measure the same construct as the task trained. However, for far-transfer tasks, transfer effects following working memory and executive function trainings are rather small.

**Cognitive Training and Neuroimaging** Several neuroimaging studies support the notion that cognitive training induces structural and functional brain changes in both younger and older adults [50]. In a recent review, Ten Brinke and collaborators [51] concluded that computerized cognitive training in healthy older adults leads to changes in brain structure, with some studies finding increased gray matter and others noting decreased cortical thickness. Changes in task-related brain activation patterns, using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have also been reported, showing patterns of increased and decreased task-related activation. Modifications in resting-state functional connectivity have also been observed following cognitive training in older adults [51].

Cognitive training studies for attentional control, working memory, or executive functions tend to report changes in functional brain activation patterns. For instance, in an fMRI study using the same dual-task cognitive training paradigm as used in Bherer et al. [34], Erickson et al. [52] reported training-induced changes in brain activity in both older and younger adults. The brain regions that showed training-induced changes were the dorsal and ventral prefrontal cortex. These cortical areas are known to be sensitive to age-related atrophy. In some regions, changes were equivalent among younger and older adults. For instance, the authors observed decreased activity in the right left ventrolateral prefrontal cortex (VLPFC) in both younger and older adults, suggesting a reduced dependence on response selection strategies or a more efficient response-stimulus association. However, age-related difference in training effect was also observed, such that older adults showed an

increased activity in the left ventrolateral prefrontal cortex (VLPFC) post-training. This may suggest an increased reliance on verbal or inner speech strategies during dual-task performance. One of the most convincing set of results reported in Erickson et al.'s [52] study is that changes in brain activation correlated with changes in task performances, suggesting that post-training brain activation patterns support more efficient behaviors.

With regard to working memory training, Brehmer et al. [53] also observed changes in neural activity with fMRI following 5 weeks of intensive adaptive and individualized working memory training. They reported reduced brain activation during the working memory task post-training, which suggests that the intervention led to more efficient neural efficiency. More recently, Heinzel et al. [54] studied the neural correlates of training and transfer effects in working memory in older adults. They compared the effect of n-back training to a no-contact control group using both the n-back task and the Sternberg task (transfer task) at pre- and post-test while BOLD signal was measured using fMRI in all participants. They observed that in the training group, the right lateral middle frontal gyrus/caudal superior frontal sulcus (Brodmann area, BA 6/8) showed reduced activation at post-training in both the trained n-back and the updating condition of the untrained Sternberg task, compared to the control group. fMRI findings also indicate a training-related increase in processing efficiency of working memory networks, potentially related to the process of working memory updating. Overall, performance gains in untrained tasks suggest that transfer effects after working memory training remain possible in aging. In a subsequent study, Heinzel et al. [55] observed that older adults having followed a 4-week working memory training not only improved their performances on the trained task, comparatively to controls, but also transferred to an untrained multi-modal dual-task (auditory and visual tasks performed concurrently). In a subgroup of participants having performed the trained n-back task while brain activation was recorded with fMRI, the authors noted that changes in neural activity in the left dorsolateral prefrontal cortex (DLPFC) during 1-back task predicted post-training auditory dual-task costs, whereas changes in neural activity in the right DLPFC during 3-back task predicted visual dual-task costs. The authors interpreted the results as a possible improvement in central executive processing.

Altogether, the results of these studies suggest that cognitive training leads to changes in brain structure and function. However, the heterogeneity of study designs, cognitive trainings, and neuroimaging techniques, as well as the infrequent reports of a correlation between behavioral improvement and changes in brain imaging results, makes it challenging to draw clear conclusions on the effects of cognitive training on brain structures and functions.

---

## Cognitive Training and Mobility Outcomes

Early cognitive or dual-task training studies were designed to explore the added benefits of training walking with an added cognitive load (see Table 17.1). In one project, Silsupadol and colleagues [56, 57] compared standard walking practice and

**Table 17.1** Single- and dual-task mobility training studies with similar outcome measures

Source	Sample(s)	Training type	Outcome measures	Key pre-post improvements
Silsupadol [56, 57]	Healthy OA	A. ST balance B. DT balance fixed priority C. DT balance variable priority	(i) ST narrow walk (ii) ST obstacle crossing (iii) DT narrow walk (iv) DT obstacle crossing. (v) ST count back (vi) ST Stroop	Cond. A, B, C for i, ii Cond. B and C for iv and v Cond. C for iii
Wongcharoen [58]	Healthy OA	A. ST balance B. ST cognition C. DT balance + cog variable priority D. DT cog + cog variable priority	(i) ST narrow walk (ii) ST obstacle crossing (iii) DT narrow walk (iv) DT obstacle crossing (v) ST fluency (vi) ST count back	Cond. B and C for i and iii
Wollesen [59]	Healthy OA	A. Balance and task management, DT walk, variable priority B. Strength training C. No-treatment	(i) ST walk (ii) DT walk (iii) ST Stroop	Cond. A > B > C for i and ii
Dorfman [60]	OA fallers	A. DT walk + cog.	(i) ST walk (ii) DT walk (iii) ST subtraction (iv) Berg balance (v) Dynamic gait (vi) Tug (vii) 6-min walk	Cond. A for i, ii, iii, iv
Mirelman [61]	Parkinson's Patients	A. Walk + cog (virtual reality) B. ST walk	(i) ST walk (ii) DT walk (iii) ST obstacles walk	Cond. A > B for i, ii, iii
De Andrade [62]	Alzheimer's Patients	A. Aerobic exercise, walk, gross motor coordination, both ST and DT B. ST walk	(i) ST balance (ii) DT balance count back (iii) DT balance tray (iv) DT balance count and tray (v) Frontal cog (vi) Functional capacity	A for i–v

Note. *OA* older adults, *ST* single-task, *DT* dual-task

dual-task walking (e.g., with concurrent mental arithmetic). Importantly, the variable priority condition (alternating focus of attention to walking or cognition) proved superior to the fixed priority condition (optimize both walking and cognition equally) and the walking only condition in terms of gains in postural control during gait. This is in line with cognitive–cognitive dual-task training studies [42]. Wongcharoen and colleagues administered a home-based version of dual-task training [58] thrice weekly for 4 weeks in a study of healthy older adults randomized to do only motor (balance) training, only cognitive training (visual attention, executive functions), simultaneous combined training (balance + cog), or simultaneous cognitive training (cog + cog). The latter two conditions were administered with varying task emphasis instructions (i.e., variable priority training). The motor-cognitive training group and cognitive only group improved on single- and dual-task narrow walking although the cognitive dual-task group did not.

Wollesen et al. [59] similarly compared cognitive-motor dual-task management training with strength training and a no-treatment control group, finding improved dual-task gait (e.g., increased step length) in the first group. Using a similar rationale, other studies have employed virtual reality gait training with older idiopathic fallers [60], Parkinson's Disease patients [61], and Alzheimer's Disease patients [62], with noted improvements on cognitive performance, functional capacity (e.g., performances in the Timed-Up-and-Go test (TUG)), and single and dual-task gait.

Overall, the strategy of adding cognitive demands to motor practice (balancing, walking) appears to be more beneficial than simple motor practice, particularly when variable priority attentional instructions are given, suggesting that training attentional flexibility might be particularly beneficial for improving mobility [63]. Of interest is the occasional finding of improved cognitive functioning alongside improvements in single- and dual-task motor performance.

**Computerized Cognitive Training** Cognitive flexibility and dual-task coordination training has also been examined in isolation using a process-based approach to cognitive training by Li and colleagues (64; see Table 17.2). The approach of training cognitive processes in isolation (i.e., seated, without walking practice) was motivated by the aim to pinpoint the purely cognitive aspects of dual-task training benefits. Basic computerized reaction time tasks (color, letter discrimination) were trained in isolation (pure blocks) and in combination (mixed blocks) during five, bi-weekly sessions of 1 hour each. The mixed blocks contained single-task trials (color task only, letter task only) intermixed randomly with dual-task trials (color and letter stimuli presented simultaneously), thus requiring cognitive flexibility. Compared to no-treatment control participants, the trained older adults significantly reduced postural sway under single-task and dual-task conditions from pre- to post-training assessments, showed improved center of pressure alignment during quiet standing, and became faster on the five times Sit-to-Stand protocol. Correlations between training-related improvements in balance and dual-task gains on the trained computer task suggested that it was process-specific dual-task training that led to the observed balance improvements (64 cf. 58).

**Table 17.2** Seated cognitive training studies with mobility outcome measures

Source	Sample(s)	Training type	Outcome measures	Key pre–post improvements
Li [64]	OA	A. Cog-cog DT B. No-treatment	(i) ST balance (ii) DT balance (iii) Sit-to-stand	Cond. A for i, ii, iii
Smith-Ray [65]	OA split by fast and slow gait	A. Multi-process cognitive B. No-treatment	(i) Tug (ii) ST gait (iii) DT gait	Cond. A for i, greater gain for slow gait subgroup for iii
Vergheze [66]	OA	A. Multi-process cognitive B. No-treatment	(i) ST gait (ii) DT gait	Cond. A for i and ii
Smith-Ray [67]	MCI or early-stage AD	A. Multi-process cognitive	(i) Tug (ii) Berg balance (iii) MMSE cog	Cond. A for i, ii, iii (trends only)

Note. *OA* older adults, *ST* single-task, *DT* dual-task, *TUG* Timed-Up-and-Go, *MMSE* Mini-mental State Examination

Similar studies of seated computerized cognitive training have been carried out using commercially available software that targets multiple cognitive processes such as divided attention, selective attention, processing speed, and working memory [65–67]. Using these multi-process training protocols, Vergheze and colleagues observed that healthy older adults who underwent training showed benefits in gait velocity and dual-task gait velocity compared to untrained controls [66]. Smith-Ray and colleagues [65, 67] used similar cognitive training software, observing improved performance on clinical measures of global mobility such as the TUG, particularly for older adults who were slow walkers [65]. A follow-up feasibility study of cognitively impaired older adults with mild-to-moderate dementia using the same cognitive training software yielded numerical improvements to TUG performance, standing balance (Berg Balance), and cognition (MMSE), although the low sample size limited the power to detect statistically significant effects [67].

**Multi-domain Training of Cognition** While seated-only cognitive training studies have yielded promising results and might be particularly useful for individuals with limited mobility, more recent cognitive training studies have examined the potential synergistic effects of combining aerobic exercise training and computerized cognitive training (see Table 17.3). Importantly, the rationale for including aerobic exercise training in this context is to improve mobility via improvements in executive functioning, rather than via improvements in lower limb strength or motor speed per se. Adding to our early computerized process-based cognitive training methods [64], a subsequent intervention study was designed to assess the benefits of combined exercise and cognitive training on single- and dual-task gait, cognition, and global mobility [68–70]. Healthy older adults were randomized to one of four training conditions that involved a computerized training activity once a week (dual-task training or internet lessons) and a physical training activity twice a week (aerobic exercise or stretch and strength) for a total of 12 weeks. Importantly, the

**Table 17.3** Multi-domain training studies with mobility outcome measures

Source	Sample(s)	Training type	Outcome measures	Key pre–post improvements
Desjardins-Crépeau [68]; Fraser [69]; Pothier [70]	Healthy OA	A. Cognitive + aerobic B. Cognitive + stretch C. Computer lessons + aerobic D. Computer lessons + stretch NB: All ST delivered on separate days	(i) TUG [68] (ii) ST walk [69] (iii) DT walk [69] (iv) Usual walk [70]	Cond. A, B, C, for i, ii, iii, iv
Bruce [71]; Lai [72]	Healthy OA	A. DT cognitive + aerobic B. ST cognitive + ST aerobic NB: Cond. B delivered on the same day	(i) ST balance [71] (ii) DT balance [71] (iii) Working memory n-back ST and DT [71] (iv) Working memory letter–number sequencing ST [72]	Cond. B for iii, iv
Jehu [74]	Healthy OA	A. ST balance and mobility B. DT balance and mobility C. No-treat control	(i) ST balance feet apart (ii) ST balance semi-tandem stance (iii) DT balance feet apart (iv) DT balance semi-tandem stance (v) DT cognition (simple, choice RT)	Cond. A and B for v
Falbo [75]	Healthy OA	A. DT motor coordination B. ST motor coordination	(i) ST walk (ii) ST obstacle clearance (iii) ST random generation	Cond. A for iii (marginal) Cond. A for i
You [76]	OA fallers	A. DT walk B. Walk with music	(i) ST memory (ii) ST walk	Cond. A for i
Eggenberger [77]	Healthy OA	A. Exergaming “DANCE” B. Stretch + balance	(i) PFC activity during walk (usual, fast) (ii) Cog executive functions	Cond. A > B for left PFC reduction
Eggenberger [78]	Healthy OA	A. Exergaming “DANCE” B. DT walk + memory C. ST walk NB: All groups also received strength and balance exercises	(i) ST gait velocity (ii) DT gait velocity (iii) ST gait variability (iv) DT gait variability (v) Falls frequency @ 6 and 12 months	Cond. A and B for ii Cond. A for i Cond. B for iii and iv Cond. A, B, C for v

(continued)



**Table 17.3** (continued)

Source	Sample(s)	Training type	Outcome measures	Key pre–post improvements
Barban [79]	OA fallers	A. ST motor B. ST motor, ST cog C. ST cognition D. Active control NB: Cond. B STs delivered on the same day	(i) POMA mobility (ii) Fear of falling (iii) Verbal memory	Cond. A and B for ii
Van het Reve [80]	OA residents	A. Strength-balance B. Strength-balance + attention	(i) DTC usual walk (ii) DTC fast walk (iii) SPPB (iv) Simple RT (v) Divided attention (vi) Fear of falling (vii) Falls at 3, 12 months post-training	Cond. B > A for i, ii, v Cond. A = B for iii, iv, vi, vii
Mirelman [81]	OA fallers MCI PD	A. Treadmill + VR B. Treadmill	(i) Incident rate of falls 6 months post-training (ii) Gait speed (iii) Gait variability (iv) Obstacle clearance (v) SPPB balance (vi) SPPB gait (vii) SF-36 physical (viii) SF-36 mental	Cond. A > B for i, ii, iii, iv, vii, viii

Note. *OA* older adults, *ST* single-task, *DT* dual-task; *DTC* dual-task cost, *RT* reaction time, *PFC* prefrontal cortex, *POMA* Tinetti's Performance Oriented Mobility Assessment, *SPPB* Short Physical Performance Battery, *VR* virtual reality, *SF-36* Short-Form Health Survey

comparison of placebo (internet, stretch) and combined treatments allowed us to determine if combined aerobic and dual-task training was superior to single-modality training. Across cognitive and motor domains, all groups showed significant improvements after training except the fourth placebo-only group (internet + stretch), but the aerobic + dual-task group did not show a significant advantage over the two intermediate conditions involving only one treatment and a one placebo. Interestingly though, this set of results also suggest that physical activity and seated computer-based dual-task cognitive training are two efficient ways to enhance usual gait speed in healthy but sedentary older adults [70].

A follow-up to the question of synergistic effects concerns the format of delivering multi-domain training: Would cognitive control and aerobic exercise training be more beneficial for cognitive-motor dual-tasking if delivered simultaneously [71, 72] rather than in succession (e.g., 69)? An argument in favor of simultaneous training is that this format might provide extra practice in multi-task coordination, and hence, be particularly helpful for complex motor behaviors like dual-task walking [57]. Conversely, simultaneously performing a motor task and a cognitive task

during training might compromise the magnitude of cognitive training gains, based on previous work showing pronounced cognitive dual-task costs in older adults (e.g., [73]). In this study, healthy older adults were randomized to receive 12 bi-weekly sessions of multi-domain training (aerobic exercise, computerized dual-task) either in sequential format (30 minutes of each per session) or simultaneously (30 minutes per session). Different from the early dual-task walking training studies [56, 57], here, recumbent bicycles and iPads were used in this study to allow for simultaneous training. Consistent with the second, cognitive interference interpretation, cognitive performance (letter–number sequencing) improved more in the sequentially trained group than the simultaneously trained group [72], as did n-back working memory performance during dual-task sit-to-stand [71]. Examination of the dual-task training data suggested a slight cognitive disadvantage for the simultaneously trained group, also in line with the cognitive interference interpretation.

Similar conclusions were reached by Jehu et al. [74] in their study of healthy older adults trained on either balance and mobility alone or with simultaneous cognitive loads. After 12 weeks of thrice-weekly training, both groups improved on their cognitive dual-tasking, but showed little improvement to postural sway during standing balance, suggesting that attentional capacity was more strongly affected than motor performance per se (see also 75, 76). Functional neuroimaging evidence using fNIRS [77] provides convergent evidence: Following 8 weeks of tri-weekly training on exergaming (DANCE) compared an active control (stretch and strength), left PFC activity was reduced when assessed during treadmill walking, signaling improved neural efficiency. These findings parallel Erickson et al.'s [52], in which older adults exhibited a downregulation of PFC activity and behavioral improvements following five sessions of computerized cognitive dual-task training [34].

**Falls Outcomes** To date, few studies have considered the benefits of simultaneous motor-cognitive training and its long-term effects on falls. One such study [78] compared cognitively intact older adults assigned to the same exergaming (DANCE) training, dual-task treadmill walking with memory training (MEMORY), and treadmill walking alone (WALK), administered twice weekly for 6 months. The three training groups showed long-term reductions in fall frequency. Interestingly, the DANCE intervention led to greater improvements in gait velocity, whereas the dual-task MEMORY intervention led to greater improvements in single- and dual-task gait variability. Together, these findings suggest that there may be process-level specificity in the gait parameters that change in each multi-component training protocol, and that either multi-domain approach can reduce falls frequency for 6–12 months following training.

A similar comparison of pure motor (gait and balance) training, cognitive (executive functions, memory), mixed cognitive and motor training (30 mins each), and control cognitive activity (data entry) was carried out in a large-scale RCT of older fallers [79]. Roughly 120 participants completed one of the four training conditions twice weekly for 12 weeks. The largest effects were observed for the mixed training group, followed by the pure motor training group in terms of fear of falling, as

measured with the Falls Efficacy Scale–International (FES-I). However, these benefits were only observed immediately after training and not at 3-month follow-up. All groups showed training benefits on verbal memory, with a slight advantage shown by the mixed training group.

In a study of seniors living in residential care [80], 182 participants were randomized to either a twice-weekly strength-balance intervention or strength-balance plus  $3 \times 10$  mins per week of attentional training (selective, sustained, and divided). Falls-related outcomes (e.g., dual-task step length mean level and variability) improved more for those who received combined motor-cognitive training compared to motor-only. However, fear of falling and falls frequency improved to an equal degree in the two groups. More encouraging in terms of falls outcomes is an RCT involving cognitively normal older adults, MCI, and PD patients with a history of falls [81]. Immersive VR treadmill walking was compared to treadmill only training. The incident rate of falls 6 months following training was more significantly reduced in the VR group than the treadmill alone group.

In sum, the literature on combined cognitive-motor training and falls reduction or fear of falling is mixed in terms of showing that an additional cognitive training component has greater benefits than physical training (strength, balance, walking) alone [78–81]. Indeed, a recent systematic review of combined exercise interventions in MCI patients revealed that no studies had reported fall rate as an outcome measure [82], suggesting that further research is needed into this question.

---

## Conclusion

The approach of training cognition, and specifically executive functions, to improve motor performance (balance, gait) and potentially prevent falls in old age, is still considered a less intuitive strategy than conventional treatments such as walking practice, motor coordination training, or balance training. From the perspective of research in the cognitive neuroscience of aging, the degree of neural and processing overlap between the trained activities and the outcome measures should affect the magnitude of training-related gains in performance [83], whether the goal of the intervention is to improve purely cognitive or motor functioning, or as is relevant to the present review, cognitive-motor dual-task performance.

The current state of knowledge in the area of aging and cognitive training research suggests that process-based cognitive training is effective for improving the cognitive performance of older adults, although the same intervention may not be as effective in older adults as in younger adults. Cognitive training protocols focused on specific processes (e.g., memory encoding, visual search) are limited in their transfer to untrained cognitive skills (i.e., poor far transfer). Exceptions to this pattern largely involve training of executive functions such as working memory updating or dividing attention. These general-purpose control processes recruit neural circuits in PFC that show neuroplasticity in older adults and younger adults [52]. Importantly, the neural overlap, or match, between such “trainable” brain regions, and those found to be relevant during walking, balancing, and dual-task motor performance, suggest an

underlying mechanism for the observed transfer effects. The strong test of this neural overlap perspective is found particularly in the studies involving only seated cognitive executive function training and motor outcomes [64–67]. As Wollesen and Voelcker-Rehage have suggested [63], transfer of training to untrained task combinations are more consistently observed when the training protocol involves combined motor and cognitive performance, although simultaneous training may delay or impair the rate of learning on the cognitive training task [71, 72].

As with much of the cognitive training literature, the mobility studies also require further investigation at present. Only a few studies include neuroimaging outcomes [77] to substantiate claims about underlying neuroplasticity driving the observed behavioral gains, and few studies include long-term follow-up data to examine the sustained effects of training. There are also few studies that consider individual differences in baseline characteristics that might affect responsiveness to training [64, 65]. Nevertheless, from the extant literature on cognitive training and mobility outcomes including falls, one strong recommendation is to build training protocols that progress in challenge adaptively for each participant. Plasticity and learning occur rapidly during an early phase and then can continue to occur more gradually as the level of challenge is adjusted according to the individual's progress [35].

Second, the inclusion of cognitive flexibility demands appears especially effective when the outcome measures include cognitive-motor dual-task performance. The flexibility can be built into multi-domain training in terms of variable priority dual-task training (e.g., 57) or in terms of the cognitive training module itself (e.g., 64). This flexibility appears to increase older adults' coordinative ability, although, to our knowledge, there has not been a study that tests this flexibility in the outcome measures. For instance, a future study design might entail outcome measures of cognitive-motor dual-tasking that alternate between instructions to adopt a posture-first and posture-second strategy of dual-tasking to determine if older adults are able to flexibly reallocate their attention when needed. Another question for future research is whether one should always expect cognitive training to improve the cognitive aspect of dual-task performance more so than the motor aspect. Based on the near-far transfer of training literature [83], one would expect cognitive training to enhance the cognitive aspect first, potentially freeing up cognitive capacity to devote to motor performance secondarily. A closer analysis of pre- versus post-training dual-task emphasis (posture-first or -second strategy) might provide a greater understanding of whether training leads to differential training gains in the cognitive or motor domain.

Finally, the research on cognitive training to improve mobility and prevent falls will continue to advance our understanding of which specific trained processes relate to specific mobility outcomes. The few studies that use individual-differences correlational analyses to examine the locus of the training benefits suggest that inhibitory control and dividing attention are associated with the magnitude of change observed through training [64, 75]. Ideally, functional neuroimaging data would provide convergent evidence for these underlying mechanisms, both while performing the specific trained cognitive task and while performing a cognitive-motor dual-task during the pre- and post-training phases.

## References

1. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60:2127–36.
2. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture*. 2002;16:1–14.
3. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329–42.
4. Baltes PB, Lindenberger U. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? *Psychol Aging*. 1997;12:12–21.
5. Lindenberger U, Baltes PB. Sensory functioning and intelligence in old age: a strong connection. *Psychol Aging*. 1994;9:339–55.
6. Bäckman L, Nyberg L, Lindenberger U, Li S-C, Farde L. The correlative triad among aging, dopamine, and cognition: current status and future prospects. *Neurosci Biobehav R*. 2006;30:791–807.
7. Lindenberger U, Ghisletta P. Cognitive and sensory declines in old age: gauging the evidence for a common cause. *Psychol Aging*. 2009;24:1–16.
8. Li KZH, Lindenberger U. Relations between aging sensory/sensorimotor and cognitive functions. *Neurosci Biobehav R*. 2002;26:777–83.
9. Schneider BA, Pichora-Fuller MK. Implications of perceptual processing for cognitive aging research. In: Craik FIM, Salthouse TA, editors. *Handbook of aging and cognition*. 2nd ed. New Jersey: Lawrence Erlbaum; 2000.
10. Beauchet O, Annweiler C, Montero-Odasso M, Fantino B, Herrmann FR, Allali G. Gait control: a specific subdomain of executive function? *J Neuroeng Rehab*. 2012;9:1–5.
11. Demnitz N, Esser P, Dawes H, Valkanova V, Johansen-Berg H, Ebmeier KP, Sexton C. A systematic review and meta-analysis of cross-sectional studies examining the relationship between mobility and cognition in healthy older adults. *Gait Posture*. 2016;50:164–74.
12. Hausdorff G, Yogev S, Springer S, Simon ES, Giladi N. Walking is more like catching than tapping: gait in the elderly as a complex cognitive task. *Exp Brain Res*. 2005;164(4):541–8.
13. Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J. The trajectory of gait speed preceding mild cognitive impairment. *Arch Neurol*. 2010;67:980–6.
14. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buschke H. Abnormality of gait as a predictor of non-Alzheimer's dementia. *New Engl J Med*. 2002;347:1761–8.
15. Montero-Odasso M, Speechley M, Muir-Hunter SW, Sarquis-Adamson Y, Sposato LA, Hachinski V, Borrie M, Wells J, Black A, Sejdic E, Bherer L, Chertkow H, Canadian Gait and Cognition Network. Motor and cognitive trajectories before dementia: results from gait and brain study. *J Am Geriatr Soc*. 2018;66:1676–83.
16. Best JR, Liu-Ambrose T, Boudreau RM, Ayonayon HN, Satterfield S, Simonsick EM, Studenski S, Yaffe K, Newman AB, Rosano C, for the Health Aging, and Body Composition Study. An evaluation of the longitudinal, bidirectional associations between gait speed and cognition in older women and men. *J Gerontol A-Med*. 2016;71:1616–23.
17. Tian Q, An Y, Resnick SM, Studenski S. The relative temporal sequence of decline in mobility and cognition among initially unimpaired older adults: results from the Baltimore Longitudinal Study of Aging. *Age Ageing*. 2017;46:445–51.
18. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. *J Gerontol A-Med*. 2014;69:1375–88.
19. Ezzati A, Katz MJ, Lipton ML, Lipton RB, Verghese J. The association of brain structure with gait velocity in older adults: a quantitative volumetric analysis of brain MRI. *Neuroradiology*. 2015;57(8):851–61.
20. Bolandzadeh N, Liu-Ambrose T, Aizenstein H, Harris T, Launer L, Yaffe K, Kritchevsky SB, Newman A, Rosano C. Pathways linking regional hyperintensities in the brain and slower gait. *NeuroImage*. 2014;99:7–13.

21. Allali G, Montembeault M, Brambati SM, Bherer L, Blumen HM, Launay CP, Liu-Ambrose T, Helbostad JL, Verghese J, Beauchet O. Brain structure covariance associated with gait control in aging. *J Gerontol A-Med Doi*. 2018; <https://doi.org/10.1093/Gerona/gly123>.
22. Abernethy B. Dual-task methodology and motor skills research: some applications and methodological constraints. *J Hum Mov Stud*. 1988;14:101–32.
23. Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y, Lipps DB. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav R*. 2010;34:721–33.
24. Holtzer R, Mahoney JR, Izzetoglu M, Onaral B, Verghese J. fNIRS study of walking and walking while talking in young and old individuals. *J Gerontol A-Med*. 2011;66:879–87.
25. Mirelman A, Maidan I, Bernard-Elazari H, Nieuwhof F, Reelick M, Giladi N, Hausdorff JM. Increased frontal brain activation during walking while dual-tasking: an fNIRS study in healthy young adults. *J NeuroEng Rehab*. 2014;11:1–7.
26. Fraser SA, Dupuy O, Pouliot P, Lesage F, Bherer L. Comparable cerebral oxygenation patterns in younger and older adults during dual-task walking with increasing load. *Front Aging Neurosci*. 2016;8:1–9.
27. Costa A, Ianez E, Ubada A, Hortal E, Del-Ama AJ, Gil-Agudo A, Axorin JM. Decoding the attentional demands of gait through EEG Gamma band features. *PLoSOne*. 2016;11:e0154136. <https://doi.org/10.1371/journal.pone.0154136>.
28. Fraizer EV, Mitra S. Methodological and interpretive issues in posture-cognition dual-tasking in upright stance. *Gait Posture*. 2008;27:271–9.
29. Huxhold O, Li S-C, Schmiedek F, Lindenberger U. Dual-tasking postural control: aging and the effects of cognitive demand in conjunction with focus of attention. *Brain Res Bull*. 2006;69:294–305.
30. Lövdén M, Schaefer S, Pohlmeier AA, Lindenberger U. Walking variability and working-memory load in aging: a dual-process account relating cognitive control to motor control performance. *J Gerontol B-Psychol*. 2008;63(3):121–8.
31. Shumway-Cook A, Baldwin M, Polissar NL, Gruber W. Predicting the probability for falls in community-dwelling older adults. *Phys Ther*. 1997;77(8):812–9.
32. Li KZH, Krampe RT, Bondar A. An ecological approach to studying aging and dual-task performance. In: Engle RW, Sedek G, von Hecker U, McIntosh DN, editors. *Cognitive limitations in aging and psychopathology: attention, working memory, and executive functions*. Cambridge, UK: Cambridge University Press; 2005.
33. Raz N, Rodrigue KM, Haacke EM. Brain aging and its modifiers. *Ann N Y Acad Sci*. 2007;1097:84–93.
34. Bherer L, Kramer AF, Peterson MS, Colcombe S, Erickson K, Becic E. Training effects on dual-task performance: are there age-related differences in plasticity of attentional control? *Psychol Aging*. 2005;20(4):695–709.
35. Bherer L, Kramer AF, Peterson MS, Colcombe S, Erickson K, Becic E. Transfer effects in task-set cost and dual-task cost after dual-task training in older and younger adults: further evidence for cognitive plasticity in attentional control in late adulthood. *Exp Aging Res*. 2008;34:1–32.
36. Kelly ME, Loughrey D, Lawlor BA, Robertson IH, Walsh C, Brennan S. The impact of cognitive training and mental stimulation on cognitive and everyday functioning of healthy older adults: a systematic review and meta-analysis. *Ageing Res Rev*. 2014;15:28–43.
37. Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Med*. 2014;11(11):e1001756.
38. National Academies of Sciences, Engineering, and Medicine. Preventing cognitive decline and dementia: a way forward. Washington, DC: The National Academies Press; 2017. <https://doi.org/10.17226/24782>.
39. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Mukadam N. Dementia prevention, intervention, and care. *Lancet*. 2017; [https://doi.org/10.1016/S0140-6736\(17\)31363-6](https://doi.org/10.1016/S0140-6736(17)31363-6).



40. Gross AL, Parisi JM, Spira AP, Kueider AM, Ko JY, Saczynski JS, Rebok GW. Memory training interventions for older adults: a meta-analysis. *Aging Ment Health*. 2012;16(6):722–34.
41. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*. 2002;288(18):2271–81.
42. Kramer AF, Larish JF, Strayer DL. Training for attentional control in dual task settings: a comparison of young and old adults. *J Exp Psychol Appl*. 1995;1:50–76.
43. Kramer AF, Larish JL, Weber TA, Bardell L. Training for executive control. *Attention Perf*. 1999;17:616–52.
44. Lussier M, Gagnon C, Bherer L. An investigation of response and stimulus modality transfer effects after dual-task training in younger and older. *Front Hum Neurosci*. 2012;6:129. <https://doi.org/10.3389/fnhum.2012.00129>.
45. Brehmer Y, Westerberg H, Backman L. Working-memory training in younger and older adults: training gains, transfer, and maintenance. *Front Hum Neurosci*. 2012;6:63. <https://doi.org/10.3389/fnhum.2012.00063>.
46. Zinke K, Zeintl M, Rose NS, Putzmann J, Pydde A, Kliegel M. Working memory training and transfer in older adults: effects of age, baseline performance, and training gains. *Dev Psychol*. 2014;50(1):304–15.
47. Karbach J, Verhaeghen P. Making working memory work: a meta-analysis of executive-control and working memory training in older adults. *Psychol Sci*. 2014;25(11):2027–37.
48. Lussier M, Brouillard P, Bherer L. Limited benefits of heterogeneous dual-task training on transfer effects in older adults. *J Gerontol B-Psychol*. 2017;72(5):801–12. <https://doi.org/10.1093/geronb/gbv105>.
49. Lussier M, Bugaiska A, Bherer L. Specific transfer effects following variable priority dual-task training in older adults. *Restor Neurol Neurosci*. 2017;35(2):237–50.
50. Belleville S, Bherer L. Biomarkers of cognitive training effects in aging. *Curr Transl Geriatr Exp Gerontol Rep*. 2012;1(2):104–10.
51. Ten Brinke LF, Davis JC, Barha CK, Liu-Ambrose T. Effects of computerized cognitive training on neuroimaging outcomes in older adults: a systematic review. *BMC Geriatr*. 2017;17(1):139.
52. Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scaf PE, Kim JS, Alvarado M, Kramer AF. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging*. 2007;28:272–83.
53. Brehmer Y, Rieckmann A, Bellander M, Westerberg H, Fischer H, Backman L. Neural correlates of training-related working-memory gains in old age. *NeuroImage*. 2011;58(4):1110–20.
54. Heinzel S, Lorenz RC, Pelz P, Heinz A, Walter H, Kathmann N, Stelzel C. Neural correlates of training and transfer effects in working memory in older adults. *NeuroImage*. 2016;134:236–49.
55. Heinzel S, Rimpel J, Stelzel C, Rapp MA. Transfer effects to a multimodal dual-task after working memory training and associated neural correlates in older adults – a pilot study. *Front Hum Neurosci*. 2017;11:85. <https://doi.org/10.3389/fnhum.2017.00085>.
56. Silsupadol P, Siu K-C, Shumway-Cook A, Woollacott MH. Training of balance under single- and dual-task conditions in older adults with balance impairment. *Phys Ther*. 2006;86:269–81.
57. Silsupadol P, Lugade V, Shumway-Cook A, van Donkelaar P, Chou L-S, Mayr U, Woollacott MH. Training-related changes in dual-task walking performance of elderly persons with balance impairment: a double-blind, randomized controlled trial. *Gait Posture*. 2009;29:634–9.
58. Wongcharoen S, Sungkarat S, Munkhetvit P, Lugade V, Silsupadol P. Home-based interventions improve trained, but not novel, dual-task balance performance in older adults: a randomized controlled trial. *Gait Posture*. 2017;52:147–52.
59. Wollesen B, Mattes K, Schulz S, Bischoff LL, Seydell L, Bell JW, von Duvillard SP. Effects of dual-task management and resistance training on gait performance in older individuals: a randomized controlled trial. *Front Aging Neurosci*. 2017;9:415. <https://doi.org/10.3389/fnagi.2017.00415>.
60. Dorfman M, Herman T, Brozgol M, Shema S, Weiss A, Hausdorff JM, Mirelman A. Dual-task training on a treadmill to improve gait and cognitive function in elderly idiopathic fallers. *J Neurol Phys Ther*. 2014;38(4):246–53. <https://doi.org/10.1097/NPT.0000000000000057>.



61. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *J Gerontol A-Med Sci*. 2011;66:234–24.
62. de Andrade LP, Gobbi LTB, Coelho FGM, Christofoletti G, Costa JLR, Stella F. Benefits of multimodal exercise intervention for postural control and frontal cognitive functions in individuals with Alzheimer's disease: a controlled trial. *J Am Geriatr Soc*. 2013;61:1919–26.
63. Wollesen B, Voelcker-Rehage C. Training effects of motor-cognitive dual-task performance in older adults. *Eur Rev Aging Phys Activity*. 2014;11:5–24.
64. Li KZH, Roudaia E, Lussier M, Bherer L, Leroux A, McKinley P. Benefits of cognitive dual-task training on balance performance in healthy older adults. *J Gerontol A-Med*. 2010;65(12):1344–52.
65. Smith-Ray RL, Hughes SL, Prohaska TR, Little DM, Jurivich DA, Hedeker D. Impact of cognitive training on balance and gait in older adults. *J Gerontol B-Psychol*. 2013;70(3):357–66.
66. Verghese J, Mahoney J, Ambrose A, Wang C, Holtzer R. Effect of cognitive remediation on gait in sedentary seniors. *J Gerontol A-Med*. 2010;65A(12):1338–43.
67. Smith-Ray RL, Irmiter C, Boulter K. Cognitive training among cognitively impaired older adults: a feasibility study assessing the potential improvement in balance. *Front Publ Health*. 2016;4:2019. <https://doi.org/10.3389/fpubh.2016.00219>.
68. Desjardins-Crépeau L, Berryman N, Fraser SA, Vu TTM, Kergoat M-J, Li KZH, Bosquet L, Bherer L. Effects of combined physical and cognitive training on fitness and neuropsychological outcomes in healthy older adults. *Clin Interv Aging*. 2016;11:1287–99.
69. Fraser SA, Li KZH, Berryman N, Desjardins-Crépeau L, Lussier M, Vadaga K, Lehr L, Minh Vu TT, Bosquet L, Bherer L. Does combined physical and cognitive training improve dual-task balance and gait outcomes in sedentary older adults? *Front Hum Neurosci*. 2017;10:688.
70. Pothier K, Gagnon C, Fraser SA, Lussier M, Desjardins-Crépeau L, Berryman N, Kergoat MJ, Vu TTM, Li K, Bosquet L, Bherer L. A comparison of the impact of physical exercise, cognitive training and combined intervention on spontaneous walking speed in older adults. *Aging Clin Exp Res*. 2017;30:921. <https://doi.org/10.1007/s40520-017-0878-5>.
71. Bruce H, Lai L, Lussier M, St. Onge N, Bherer L, Li KZH. Combined exercise and cognitive training to improve auditory working memory and mobility in older adults. *Gait Posture*. 2019;67:262–8.
72. Lai L, Bruce H, Bherer L, Lussier M, Li KZH. Comparing the transfer effects of simultaneous and sequential combined aerobic exercise and cognitive training in older adults. *J Cogn Enhanc*. 2017;1:478–90.
73. Li KZH, Lindenberger U, Freund AM, Baltes PB. Walking while memorizing: age-related differences in compensatory behavior. *Psychol Sci*. 2001;12:230–7.
74. Jehu D, Paquet N, Lajoie Y. Balance and mobility training with or without concurrent cognitive training does not improve posture, but improves reaction time in healthy older adults. *Gait Posture*. 2017;52:227–32.
75. Falbo S, Condello G, Capranica L, Forte R, Pesce C. Effects of physical-cognitive dual task training on executive function and gait performance in older adults. A randomized controlled trial. *BioMed Research International*. 2016. <https://doi.org/10.1155/2016/5812092>.
76. You JH, Shetty A, Jones T, Shields K, Belay Y, Brown D. Effects of dual-task cognitive-gait intervention on memory and gait dynamics in older adults with a history of falls: a preliminary investigation. *NeuroRehab*. 2009;24:193–8. <https://doi.org/10.3233/NRE-2009-0468>.
77. Eggenberger P, Wolf M, Schumann M, de Bruin ED. Exergame and balance training modulate prefrontal brain activity during walking and enhance executive function in older adults. *Front Aging Neurosci*. 2016;8:66. <https://doi.org/10.3389/fnagi.2016.00066>.
78. Eggenberger P, Theill N, Holenstein S, Schumacher V, de Bruin E. Multicomponent physical exercise with simultaneous cognitive training to enhance dual-task walking of older adults: a secondary analysis of a 6-month randomized controlled trial with 1-year follow-up. *Clin Interv Aging*. 2015;10:1711–32.
79. Barban F, Annicchiarico R, Melideo M, Federici A, et al. Reducing fall risk with combined motor and cognitive training in elderly fallers. *Brain Sci*. 2017;7:19.

80. van het Reve E, de Bruin ED. Strength-balance supplemented with computerized cognitive training to improve dual task gait and divided attention in older adults: a multicenter randomized-controlled trial. *BMC Geriatr.* 2014;14:134. <https://doi.org/10.1186/1471-2318-14-134>.
81. Mirelman A, Rochester L, Maidan I, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet.* 2016;388:1170–82.
82. Lipardo DS, Aseron AMC, Kwan MM, Tsang WW. Effect of exercise and cognitive training on falls and fall-related factors in older adults with mild cognitive impairment: a systematic review. *Arch Phys Med Rehab.* 2017;98:2079–96.
83. Lustig C, Shah P, Seidler R, Reuter-Lorenz PA. Aging, training, and the brain: a review and future directions. *Neuropsychol Rev.* 2009;19:504–22.



# Virtual Reality Training as an Intervention to Reduce Falls

# 18

Anat Mirelman, Inbal Maidan, Shirley Shema Shiratzky,  
and Jeffrey M. Hausdorff

## Motor and Cognitive Function and Their Association with Falls

Falls result from interactions between multiple individual and environmental risk factors. Extensive research has identified many risk factors in older people in the community, including previous falls, demographic characteristics (such as female sex and older age), health habits, pain, chronic neurological and musculoskeletal diseases, medications, physical impairments, functional limitations, disabilities, and environmental barriers [1]. Most falls occur during walking and not surprisingly, gait impairments have been associated with an increased risk of falls [2–4]. With aging, elderly individuals generally walk more slowly, with shorter strides,

---

A. Mirelman (✉) · I. Maidan

Laboratory for Early Markers Of Neurodegeneration (LEMON), Neurological Institute,  
Tel Aviv Medical Center, Tel Aviv, Israel

Center for the Study of Movement, Cognition and Mobility, Neurological Institute,  
Tel Aviv Medical Center, Tel Aviv, Israel

Sackler Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University,  
Tel Aviv, Israel

e-mail: [anatmi@tlvmc.gov.il](mailto:anatmi@tlvmc.gov.il)

S. S. Shiratzky

Center for the Study of Movement, Cognition and Mobility, Neurological Institute,  
Tel Aviv Medical Center, Tel Aviv, Israel

J. M. Hausdorff

Center for the Study of Movement, Cognition and Mobility, Neurological Institute,  
Tel Aviv Medical Center, Tel Aviv, Israel

Department of Physical Therapy, Sackler Faculty of Medicine and Sagol School of  
Neuroscience, Tel Aviv University, Tel Aviv, Israel

Rush Alzheimer's Disease Center and Department of Orthopaedic Surgery,  
Rush University Medical Center, Chicago, IL, USA

e-mail: [jhausdor@tlvmc.gov.il](mailto:jhausdor@tlvmc.gov.il)

decreased arm swing and longer double limb support times, and increased stride-to-stride variability [2, 5]. These deficits that are exacerbated in elderly fallers [2, 5], although it is not yet fully clear if these gait changes lead to an increased fall risk or if they are a maladaptive response to falls. Nonetheless, biomechanical processes and falls were, in the past, largely viewed as a failure of gait and balance mechanisms.

Exercise, aimed at improving gait and balance impairments in older adults, reduces the rate and risk of falls [1, 6, 7]. A recent meta-analysis of 88 trials for fall prevention [7] with 19,478 participants demonstrated that exercise reduced the rate of falls in community-dwelling older people by 21%, with greater effects seen from exercise programs that challenged balance and involved more than 3 hours per week of exercise. These findings are based on studies in older adults without significant cognitive impairments. It is now well accepted that cognitive impairment not only increases the risk of falls but may also adversely affects adherence to interventions and the effectiveness of such interventions. Results from fall prevention trials in cognitively intact older people should not be generalized to those with cognitive impairment [1, 8].

Indeed, attributing falls in older individuals only to motor and sensory impairments is overly simplistic. Research over the last decades has clearly demonstrated the strong connection between balance, gait and falls, on the one hand, and cognitive function, on the other hand [9–14]. Dementia and falls often coexist in older adults, gait impairments and falls are more prevalent in individuals with dementia than in those with normal cognitive aging, and this prevalence increases with the severity of cognitive impairment [13]. Specifically the cognitive subdomains of attention and executive function (EF) have been linked to gait alterations and fall risk [9, 10, 12, 15, 16]. For example, worse EF scores at baseline were associated with falls that occurred during a 2-year follow-up among healthy participants who reported no falls at baseline [9]. This relationship makes sense considering the role of EF in task planning, dual tasking, sensory integration, judgment, and reasoning [14, 16]. Dual-task-related gait changes partly depend on the capacity to allocate attention between two tasks performed simultaneously and are mainly related to executive dysfunction.

EF and attention abilities are reduced with aging, placing older adults at higher risk of falling when they attempt to perform two or more tasks simultaneously [17, 18]. These negative effects of aging are even larger among elderly fallers than in the general elderly population [9, 19, 20]. These findings have important implications on every day function. They support the idea that when people are distracted or attempt to perform a task that diverts attention from walking or stepping [19], gait deficits become exacerbated, walking becomes less safe, and the risk of falls increases. Attention and planning are also associated with complex everyday life activities such as obstacle negotiation. Older adults and patients with neurodegenerative conditions often have difficulties with negotiating obstacles, with the lower leg of older adults passing dangerously close to impediments during walking [21, 22].

Due to the multifaceted aspects of falls [23–25], it is only reasonable to posit that therapeutic interventions aimed at reducing fall risk should be designed to address

both motor and cognitive aspects of safe gait while also addressing dynamic balance and muscle strength deficits [1, 8, 13, 26–28]. Multifactorial interventions involve several modalities and are usually provided by multidisciplinary professionals. The interventions may include exercise, review and modification of medications, and/or addressing risk factors and home adjustments, and referrals. Physical therapy (PT) is considered a multifactorial intervention as it may include several training modalities. As mentioned above, exercise has become a widely studied fall prevention intervention. However, despite the increasing recognition of the importance of cognition, motor, and obstacle negotiation abilities, multifactorial interventions have generally focused on individual risk factors separately, largely ignoring their interdependence and the role of executive function, attention, and cognitive function, more generally.

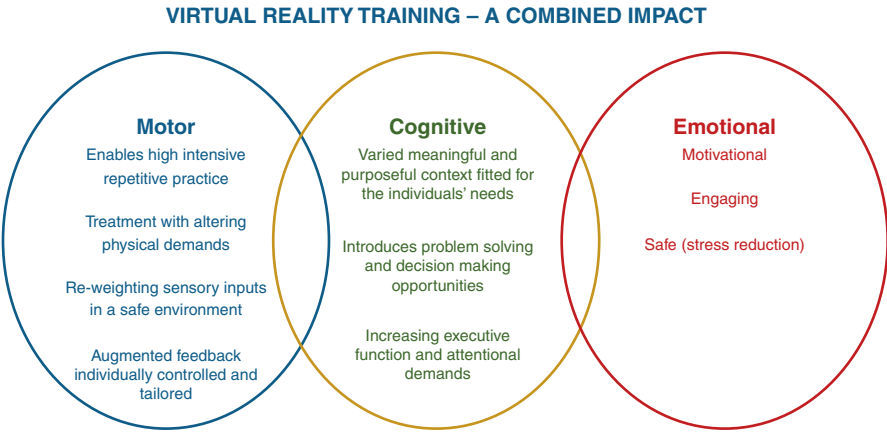
---

## Virtual Reality for Motor-Cognitive Training

Virtual reality (VR) is defined as a high-end computer interface that involves real time simulation and interactions through multiple sensory channels [26, 29]. The impetus for using VR for motor-cognitive training is that the technology may enable individualized repetitive practice of motor function, graded in accordance to the needs and level of ability of the person, while engaging in and stimulating cognitive processes, typically in a fun, game-like environment. VR can be used to provide training in a more stimulating and enriching environment than traditional rehabilitation, while providing feedback about performance to assist with the learning of new motor strategies of movement. The realism of the virtual environments provides individuals with the opportunity to safely explore their environments, increasing their sense of autonomy and independence in directing their own therapeutic experience.

VR training can also address emotional aspects. It is challenging and enjoyable which makes the intervention engaging and motivating, VR training can also reduce fear or anxiety of performance and improve exercise compliance and effectiveness in patients with different affective disorders and motor impairments [30–32]. These VR qualities allow for higher intensity of training in short duration protocols with relatively low patient burden [29, 33]. VR protocols can be standardized and replicated and enable domain-specific or multidomain progression, fostering a personalized medicine approach. Based on these many beneficial attributes, VR technology can be well suited to address the multiple motor, cognitive, and emotional aspects required to reduce the risk of falls [24, 26, 33] (Fig. 18.1).

In recent years, there has been a spurt of technological advancement. VR systems have become more affordable and portable allowing for use even in the home environment by unprofessional personnel. Systems differ with respect to their interface and simulation content, the latter is generally chosen to fit the specific goals of the VR intervention. Interfaces to the VR simulation could include a screen and motion camera [26, 34], head-mounted displays or glasses, and include both custom-made and commercially available systems specifically designed for older adults (Fig. 18.2).



**Fig. 18.1** Virtual reality attributes. A combined motor, cognitive, and emotional impact



**Fig. 18.2** Different virtual reality systems used for motor-cognitive interventions for the elderly. From the left, a commercial system (Dance–Dance Revolution) [26], the oculus rift head-mounted display [35], and a custom-made system: V-TIME [34]

As previously mentioned, fall prevention interventions should include multiple aspects relating to falls, task-specific and generalized training. The intervention should be centered around the user’s needs while applying principles of motor learning to teach new strategies that can be applied in different everyday settings and situations to decrease fall risk [24, 26, 29]. VR can be used as a gateway to functional recovery in the elderly as it allows for the simultaneous focusing on both the physical and cognitive domains to decrease the risk of falls and empower safe community ambulation and function [24, 26]. This approach has the potential to

address many of the barriers that currently prevent adaptation of other fall risk treatment programs in clinical settings (e.g., poor compliance to the intervention, poor retention after training, costly, not readily available, and not engaging). Whereas other forms of exercise interventions may be viewed as a boring, highly repetitive burden, VR is fun and challenging, promoting long-term compliance [36].

---

## Virtual Reality for Reducing Falls

A recent meta-analysis summarized evidence on the effectiveness of virtual reality games as compared to conventional therapy or no intervention for improving motor function in the elderly. A total of 28 studies were evaluated among 1121 elderly participants. The study found that VR games significantly improved mobility, balance, and fear of falling after 3–6 and 8–12 weeks of intervention when compared with no intervention and had superior effects on balance improvements (as measured using the Berg balance test), compared to conventional interventions [37].

In addition to the studies that examined the effects of VR on mobility and balance, several studies explored the utility of VR for specifically reducing fall frequency or fall risk (i.e., using fall rate as a primary outcome measure). In one of the earlier studies, Duque et al. [38] evaluated the use of a Balance Rehabilitation Unit (BRU) implemented with VR in 70 older adults with a history of falls (mean  $3.4 \pm 3$  falls in 6 months prior to the study). The BRU is a balance platform combined with visual display presented in front of the user. Participants received either the BRU-training which included two sessions of balance training per week for 6 weeks each lasting 30 minutes or usual care which included an invitation to join an exercise program (following the Otago protocol), medication review, home visit by an occupational therapist, hearing and visual assessment, vitamin D supplementation, and education materials on falls prevention. Both groups showed a significant reduction in the incidence of falls. However, 9 months after the intervention, BRU-training subjects reported a significantly lower number of falls as compared with the controls ( $1.1 \pm 0.7$  vs.  $2.0 \pm 0.2$ , respectively) and lower levels of fear of falling [38].

Similar findings were observed by Fu et al. [39]. They compared the effects of a 6-week training program (three times a week) of VR, provided by the Nintendo Wii Fit, to conventional strength and stretching exercises on incidence of falls in 60 older adults living in a nursing home. The incidence of falls, measured over the 12 months after the completion of the intervention, improved significantly in both groups. Nonetheless, participants in the Wii Fit training group showed a significantly greater improvement compared to the control group. The results suggest that even in institutionalized older adults with a history of falls, VR training can be used to effectively reduce fall risk and the incidence of falls [39].

Another study using the Wii Fit balance exercises explored the utility of this method for the training of individuals post stroke [40]. The researchers compared the effects of training twice weekly for 10 weeks with the Wii fit compared to a similar dose of conventional physical therapy sessions including stretching, strengthening, and balance exercises. Although there was a significant effect on falls



in the VR group after training, the median number of falls prior to the evaluation was small (0–1 or 0–2 in the experimental group and the control group, respectively). Thus, although the findings are encouraging, future studies should explore the value of VR in reducing fall incidence in a larger sample of individuals post stroke [40].

Eggenberger et al. [23] investigated the added value of the VR component as compared to a motor-cognitive intervention and a motor intervention alone. Eighty-nine participants were randomized to three groups: (1) virtual reality video game dancing (DANCE), (2) treadmill walking with simultaneous verbal memory training (MEMORY), or (3) treadmill walking (PHYS). Each program was delivered twice weekly for 20 minutes followed by strength and balance exercises for the duration of 6 months. Fall rates were evaluated for 1-year post intervention. Both motor-cognitive interventions (DANCE and MEMORY) showed a significant advantage in dual task cost and gait variability, proxies of fall risk. Fall frequency was significantly reduced by 77%, from 0.79 falls per person-year at baseline to 0.18 falls per person-year during the first 6-month period after training. However, there was no difference between the training arms [23]. This could potentially be attributed to the small number of participants and the large variability in the number of falls.

Parijat et al. [41] used a head-mounted display to provide a virtual reality scene of a street environment. The VR scene consisted of virtual slips or perturbations (tilts) in the pitch plane at random intervals while participants walked on the treadmill. The researchers investigated whether this type of training is useful in teaching older adults a strategy to avoid slips. Participants received three training sessions using the system while participants in the control group received standard gait training. During evaluations, participants were asked to walk on a slippery surface covered with a 1:1 water and KY-Jelly mixture while wearing a harness. A slip trial was considered a fall if the slip distance exceeded 10 cm, peak sliding heel velocity exceeded the whole body center of mass velocity while slipping, and the participant's body dropped toward the floor after slipping and arrested by the harness before impact. The VR group was able to reduce the frequency of falls from 50% at baseline to 0% in the transfer of training trial, suggesting improved reactive changes after slip. This effect was not observed in the control group. The VR training also had beneficial effects in improving recovery reactions in older adults when encountering a slippery surface, also suggestive of a reduced fall risk [41].

The abovementioned trials (as summarized in Table 18.1) demonstrate the feasibility of using VR for reducing falls and fall risk in older adults in single-center studies with a relatively small number of participants. The V-TIME study [29, 34] is, to date, the largest multicenter randomized controlled trial to directly investigate the use of a VR training approach for the reduction of falls. It examined the effects of VR training in 282 older adults who had a high risk of falls based on a history of two or more falls in the 6 months before the study. Participants included older adults with a history of falls (idiopathic fallers), patients with Parkinson's disease, and individuals with mild cognitive impairments with a history of multiple falls. Subjects were randomly assigned to receive 6 weeks of either treadmill training plus VR or

**Table 18.1** Summary of studies that specifically examined the impact VR-based interventions on falls in older adults

Citation	Population			Interventions			Results related to falls	
	Condition	Group = N	Age (years)	Type	Sequence	Dose (min/frq/wks)		
da Fonseca (2017)	Patients post-stroke	EXP = 15 CON = 15	53.8 ± 6.3 50.9 ± 10.9	Nintendo Wii fit balance training Conventional physiotherapy	Warm up followed by games of tennis, hula-hoop, soccer, and boxing Stretching, trunk mobilization, standing balance training, and free gait training	60/2/10 60/2/10	No. of falls was significantly reduced only in the EXP group ( $p = 0.049$ ). The between-group comparison of fall frequency was not significant. No follow-up was performed	
Duque (2013)	Elderly fallers	EXP = 30 CON = 40	79.3 ± 10 75.0 ± 8.0	Visual-vestibular rehabilitation and postural training VR exercises + usual care Usual care alone	Exercises include three different postural training games with increasing levels of complexity Recommendations regarding exercise, medication review, nutrition, visual and hearing assessment, and home visit by an OT	30/2/6 N/A	After 9 months of follow-up, both groups showed a significant reduction in the incidence of falls ( $P < 0.05$ ) Subjects in the EXP group reported a significantly lower no. of falls as compared with the untrained controls ( $1.1 \pm 0.7$ in the EXP group vs. $2 \pm 0.2$ in the CON group; $P < 0.01$ )	

(continued)

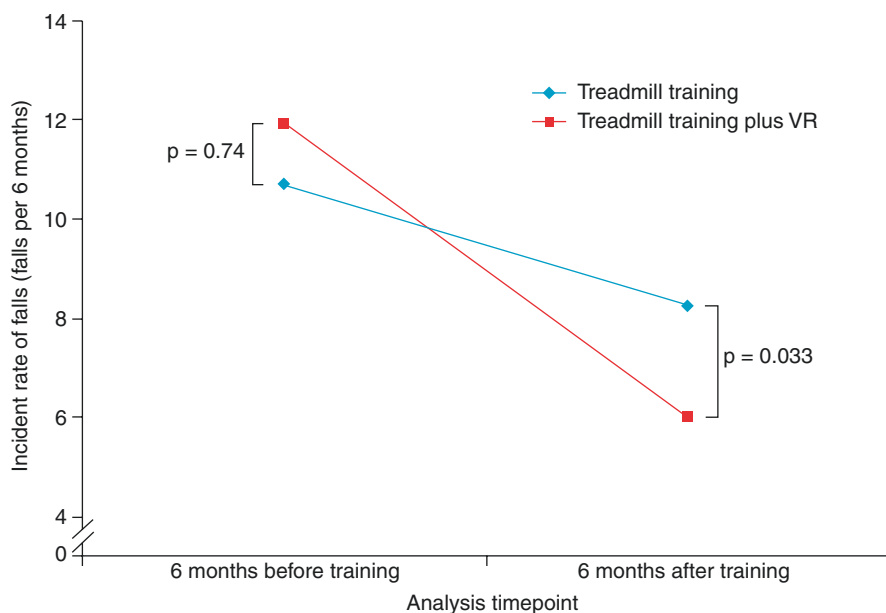
**Table 18.1** (continued)

Citation	Population	Interventions			Dose (min/frq/wks)	Results related to falls
	Condition	Group = N	Age (years)	Type	Sequence	
Eggenberger (2015)	Older adults, cognitive intact (age > 70 years)	DANCE = 24 MEM = 22 PHYS = 25	77.3 ± 6.3 78.5 ± 5.1 80.8 ± 4.7	VR dancing game Treadmill training + verbal memory task Treadmill training alone	Subjects performed stepping sequence on pressure sensitive platforms, in response to visual cues, and according to musical rhythm Treadmill walking while memorizing a sequence of 3 to 20 word list Treadmill walking or running at a constant pace	Frequency of falls was reduced 6 months after the training, as compared to 6 months before the training ( $p < 0.001$ ) No differences were found between the three interventions
Fu (2015)	Older adults living in a nursing home	EXP = 30 CON = 30	82.4 ± 3.8 82.3 ± 4.3	Nintendo Wii fit balance training Conventional balance training	Subjects played games (soccer head, table tilt, and bubble balance) that require weight shifting, manipulating objects while standing and kicking Lower limb strength, tandem standing, and walking, stepping and sit-to-stand exercise, half squats	Incidence of falls over 12 months of follow-up was significantly reduced posttraining in both training arms Baseline no. of falls was comparable between groups. After the training, subjects in the EXP group experienced significantly less falls compared to the CON group ( $p < 0.001$ )

Parijat (2015)	Healthy older adults	EXP = 12 CON = 12	70.5 ± 6.6 74.2 ± 5.8	Treadmill walking + VR Usual walking over ground	Subjects walked on a treadmill wearing a HMD. Virtual environment of a street introduced virtual slips (perturbations in the Pitch plane of the VR scene) at random intervals Subjects walked on a walkway for 15 minutes X three trials	55/1/1 45/1/1	The EXP group was able to reduce the frequency of slip-induced falls from 50% at baseline to 0% after the training ( $p = 0.03$ ). Although the frequency of falls in the CON group reduced from 50% at baseline to 25% posttraining, the difference was not significant ( $p = 0.216$ )
Mirelman (2016)	Older adults with recent fall history, including elderly fallers, patients with MCI and people with PD	EXP = 146 CON = 136	74.2 ± 6.9 73.3 ± 6.4	Treadmill training + VR Treadmill training alone	Subjects walked on a treadmill while negotiating virtual obstacles. Level of difficulty was gradually progressed Conventional treadmill walking	45/3/6 45/3/6	Before training, the incident rate of falls was similar in both groups In the 6 months after training, the incident rate was significantly lower in the EXP group than it had been before training ( $p < 0.0001$ ), whereas the incident rate did not decrease significantly in the CON group ( $p = 0.49$ )

treadmill training alone. Both groups trained three times per week for 6 weeks, with each session lasting about 45 min and with training progression individualized to the participant's level of performance. The VR system consisted of a motion-capture camera and a computer-generated simulation projected on to a large screen, including real-life challenges such as obstacles, multiple pathways, and distracters that required continual adjustment of steps (recall Fig. 18.2c). The primary outcome was the incident rate of falls during the 6 months after the end of training.

At 6 months after training, both treadmill training interventions significantly improved markers of fall risk and fall rates were lowered for both interventions, compared with the values from before training, emphasizing the therapeutic value of the active control intervention (i.e., treadmill training alone) [29, 34]. Nonetheless, comparisons within the training groups showed that the reduction in fall rates was only significant in the treadmill training plus VR group (a 55% reduction) and not in the treadmill-training group. Consistent with this finding, a direct comparison of the two training groups showed that the treadmill training plus VR intervention had a significant, positive effect on the incident rate of falls; the rate of falls after training was 42% lower in the treadmill training plus VR arm than in the active control group (Fig. 18.3). The training also had a positive effect on fall risk measures (gait variability during obstacle negotiation and obstacle clearance), improving both to a larger degree than that seen in those who trained on the treadmill without the virtual reality component. The added value of the VR component might be explained by the nature of the training. The motor-cognitive intervention provided by the VR implicitly trained obstacle negotiation strategies in a complex, enriched environment that



**Fig. 18.3** Differences in fall rate before and after training in the V-TIME study [29, 34]

requires focused attention and planning, in a VR environment that mimics everyday walking in the real world and implicitly teaches safe ambulation. Indeed, participants also reported more engagement and satisfaction by the training and reported that they felt more confident [36]. The findings further support the notion that a combined motor-cognitive intervention could be beneficial to reduce fall rates in older adults and those with neurodegenerative conditions [42].

---

## Discussion and Future Directions

The findings from the VR literature on reduction of fall rate in response to intervention are in line with the most effective fall preventions that have assessed more traditional group-based and home-based exercise interventions in older people and well above the average reduction of 21% for exercise interventions reported in systematic reviews [7]. This could be a result of the interactive environments, which are engaging and enable long duration practice with increased level of challenge. These systems have the potential to influence postural control and fall events by stimulating the sensory cues that are needed for maintaining balance and orientation and by improving motor control patterns as well as cognitive functions and emotional aspects. VR also enables training in high intensity in simulations that are ecologically valid, resembling everyday life situations and allows for training that focuses on the key motor-cognitive aspects that are critical to safe ambulation. It is possible that the positive effects observed in studies with VR are related to improved multitasking and gait adaptability in situations requiring focused attention and planning and these in turn transfer to real-world situation.

The field of VR for falls is still relatively young, with only a limited number of studies specifically examining the effects of VR training on falls in older adults. Future research should explore different populations including older adults with cognitive impairments. Much is still unknown regarding the optimal dosing and intensity of training required to impact falls in older adults and the retention of these effects (beyond what is reported today). In addition, it is imperative to evaluate the effectiveness of this method in clinical instead of research settings, fully evaluating the utility of this approach administered in community gyms and rehabilitation clinics. Lastly, it will be interesting to examine whether this method could be used as part of a fall prevention approach, to treat fall risk before falls become common (i.e., “prehab”) and before any injuries occur.

---

## References

1. Vieira ER, Palmer RC, Chaves PH. Prevention of falls in older people living in the community. *BMJ*. 2016;353:i1419.
2. Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil*. 2001;82(8):1050–6.
3. Robinovitch SN, Feldman F, Yang Y, Schonnop R, Leung PM, Sarraf T, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet*. 2013;381(9860):47–54.

4. Sartini M, Cristina ML, Spagnolo AM, Cremonesi P, Costaguta C, Monacelli F, et al. The epidemiology of domestic injurious falls in a community dwelling elderly population: an out-growing economic burden. *Eur J Pub Health*. 2010;20(5):604–6.
5. Legters K. Fear of falling. *Phys Ther*. 2002;82(3):264–72.
6. Sherrington C, Tiedemann A, Fairhall N, Close JC, Lord SR. Exercise to prevent falls in older adults: an updated meta-analysis and best practice recommendations. *N S W Public Health Bull*. 2011;22(3–4):78–83.
7. Sherrington C, Michaleff ZA, Fairhall N, Paul SS, Tiedemann A, Whitney J, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. *Br J Sports Med*. 2017;51(24):1750–8.
8. Winter H, Watt K, Peel NM. Falls prevention interventions for community-dwelling older persons with cognitive impairment: a systematic review. *Int Psychogeriatr*. 2013;25(2):215–27.
9. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci*. 2010;65(10):1086–92.
10. Mirelman A, Herman T, Brozgol M, Dorfman M, Sprecher E, Schweiger A, et al. Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. *PLoS One*. 2012;7(6):e40297.
11. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60(11):2127–36.
12. Montero-Odasso M, Hachinski V. Preludes to brain failure: executive dysfunction and gait disturbances. *Neurol Sci*. 2014;35(4):601–4.
13. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: implications for risk assessment and prevention. *J Am Geriatr Soc*. 2018;66(2):367–75.
14. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299–308.
15. Holtzer R, Ozelius L, Xue X, Wang T, Lipton RB, Verghese J. Differential effects of COMT on gait and executive control in aging. *Neurobiol Aging*. 2010;31(3):523–31.
16. Liu-Ambrose T, Davis JC, Nagamatsu LS, Hsu CL, Katarynych LA, Khan KM. Changes in executive functions and self-efficacy are independently associated with improved usual gait speed in older women. *BMC Geriatr*. 2010;10:25.
17. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. *Mov Disord*. 2013;28(11):1520–33.
18. Hausdorff JM, Schweiger A, Herman T, Yogev-Seligmann G, Giladi N. Dual-task decrements in gait: contributing factors among healthy older adults. *J Gerontol A Biol Sci Med Sci*. 2008;63(12):1335–43.
19. Alexander NB, Hausdorff JM. Guest editorial: linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci*. 2008;63(12):1325–8.
20. Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. *J Am Geriatr Soc*. 2009;57(2):359–60.
21. Galna B, Murphy AT, Morris ME. Obstacle crossing in people with Parkinson's disease: foot clearance and spatiotemporal deficits. *Hum Mov Sci*. 2010;29(5):843–52.
22. Maidan I, Eyal S, Kurz I, Geffen N, Gazit E, Ravid L, et al. Age-associated changes in obstacle negotiation strategies: does size and timing matter? *Gait Posture*. 2018;59:242–7.
23. Eggenberger P, Theill N, Hostenstein S, Schumacher V, de Bruin ED. Multicomponent physical exercise with simultaneous cognitive training to enhance dual-task walking of older adults: a secondary analysis of a 6-month randomized controlled trial with 1-year follow-up. *Clin Interv Aging*. 2015;10:1711–32.
24. Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with Parkinson's disease? *J Gerontol A Biol Sci Med Sci*. 2011;66(2):234–40.
25. Rosso AL, Studenski SA, Chen WG, Aizenstein HJ, Alexander NB, Bennett DA, et al. Aging, the central nervous system, and mobility. *J Gerontol A Biol Sci Med Sci*. 2013;68(11):1379–86.



26. de Bruin ED, Schoene D, Pichierri G, Smith ST. Use of virtual reality technique for the training of motor control in the elderly. Some theoretical considerations. *Z Gerontol Geriatr*. 2010 Aug;43(4):229–34.
27. Canning CG, Sherrington C, Lord SR, Close JC, Heritier S, Heller GZ, et al. Exercise for falls prevention in Parkinson disease: a randomized controlled trial. *Neurology*. 2015;84(3):304–12.
28. Varma VR, Hausdorff JM, Studenski SA, Rosano C, Camicioli R, Alexander NB, et al. Aging, the central nervous system, and mobility in older adults: interventions. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1451–8.
29. Mirelman A, Rochester L, Reelick M, Nieuwhof F, Pelosin E, Abbruzzese G, et al. V-TIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled trial. *BMC Neurol*. 2013;13:15.
30. Ehgoetz Martens KA, Ellard CG, Almeida QJ. Does anxiety cause freezing of gait in Parkinson's disease? *PLoS One*. 2014;9(9):e106561.
31. Levy F, Leboucher P, Rautureau G, Komano O, Millet B, Jouvent R. Fear of falling: efficacy of virtual reality associated with serious games in elderly people. *Neuropsychiatr Dis Treat*. 2016;12:877–81.
32. McCann RA, Armstrong CM, Skopp NA, Edwards-Stewart A, Smolenski DJ, June JD, et al. Virtual reality exposure therapy for the treatment of anxiety disorders: an evaluation of research quality. *J Anxiety Disord*. 2014;28(6):625–31.
33. Cherniack EP. Not just fun and games: applications of virtual reality in the identification and rehabilitation of cognitive disorders of the elderly. *Disabil Rehabil Assist Technol*. 2011;6(4):283–9.
34. Mirelman A, Rochester L, Maidan I, Del DS, Alcock L, Nieuwhof F, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet*. 2016;388(10050):1170–82.
35. Saldana SJ, Marsh AP, Rejeski WJ, Haberl JK, Wu P, Rosenthal S, et al. Assessing balance through the use of a low-cost head-mounted display in older adults: a pilot study. *Clin Interv Aging*. 2017;12:1363–70.
36. Dockx K, Alcock L, Bekkers E, Ginis P, Reelick M, Pelosin E, et al. Fall-prone older People's attitudes towards the use of virtual reality technology for fall prevention. *Gerontology*. 2017;63(6):590–8.
37. Neri SG, Cardoso JR, Cruz L, Lima RM, de Oliveira RJ, Iversen MD, et al. Do virtual reality games improve mobility skills and balance measurements in community-dwelling older adults? Systematic review and meta-analysis. *Clin Rehabil*. 2017;31(10):1292–304.
38. Duque G, Boersma D, Loza-Diaz G, Hassan S, Suarez H, Geisinger D, et al. Effects of balance training using a virtual-reality system in older fallers. *Clin Interv Aging*. 2013;8:257–63.
39. Fu AS, Gao KL, Tung AK, Tsang WW, Kwan MM. Effectiveness of exergaming training in reducing risk and incidence of falls in frail older adults with a history of falls. *Arch Phys Med Rehabil*. 2015;96(12):2096–102.
40. Pedreira da FE, Ribeiro da Silva NM, Pinto EB. Therapeutic effect of virtual reality on post-stroke patients: randomized clinical trial. *J Stroke Cerebrovasc Dis*. 2017;26(1):94–100.
41. Parijat P, Lockhart TE, Liu J. Effects of perturbation-based slip training using a virtual reality environment on slip-induced falls. *Ann Biomed Eng*. 2015;43(4):958–67.
42. Dockx K, Bekkers EM, Van den Bergh V, Ginis P, Rochester L, Hausdorff JM, et al. Virtual reality for rehabilitation in Parkinson's disease. *Cochrane Database Syst Rev*. 2016;12:CD010760.

# Cognitive Enhancers as a Means to Reduce Falls in Older Adults

# 19

Nicolaas I. Bohnen and Martijn L. T. M. Müller

## Abbreviations

AD	Alzheimer disease
MCI	mild cognitive impairment
PD	Parkinson disease
PDD	Parkinson disease with dementia
PPN	pedunculopontine nucleus

## Introduction

The etiology of falls in the elderly is multifactorial, including both intrinsic (e.g., muscle weakness) and extrinsic (e.g., ground surfaces) risk factors. Studies have

---

N. I. Bohnen (✉)

Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Department of Neurology, University of Michigan, Ann Arbor, MI, USA

Veterans Administration Ann Arbor Healthcare System, Ann Arbor, MI, USA

Morris K. Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor, MI, USA

Functional Neuroimaging, Cognitive and Mobility Laboratory, University of Michigan, Domino's Farms, Ann Arbor, MI, USA

e-mail: [nbohn@umich.edu](mailto:nbohn@umich.edu)

M. L. T. M. Müller

Department of Radiology, University of Michigan, Ann Arbor, MI, USA

Morris K. Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor, MI, USA

e-mail: [mtmuller@umich.edu](mailto:mtmuller@umich.edu)

found that cognitive impairment, visual deficits, lower extremity dysfunction, slow gait, previous falls, depression, neuropathy, and polypharmacy are all important risk factors for falls [46, 61, 68, 75, 77]. There is also evidence of a synergistic interaction between these different risk factors. Importantly, the risk of falling increases sharply with the presence of more risk factors. For example, 65–100% of elderly persons with 3 or more risk factors fell in a 1-year period, compared with 8–12% of persons without risk factors [61, 67]. It should be noted that although specific risk factors may be associated with falling, the general health of an individual, including central reflex mechanisms and motor skills (postural reserve capacity), may strongly aid in the prevention of falls [84]. Impairments of the nervous system appear to be a key contributory role to fall risk in older adults.

Elderly with cognitive impairment have a more than two times higher fall risk compared to cognitively normal subjects [25, 77]. The same applies for Parkinson disease (PD). For example, the incidence of falls for patients with PD has been reported as 24.1% for those with normal cognition, 43.8% in patients with mild cognitive impairment (MCI), and 63.6% in PD dementia [43]. A prospective study of healthy controls, PD, AD, dementia with Lewy bodies and vascular dementia patients found that demented neurodegenerative subjects experienced nearly 8 times more incident falls than controls [2]. Cognitive deficits, in particular deficits in executive function and attention, may be important risk factors for falls not only in PD but also in the elderly [31]. One of the earliest reports came from Lundin-Olsson and colleagues who in a thought-provoking brief report [45] described that institutionalized elderly persons who were unable to maintain a routine conversation while walking had a high risk of falls (“stops walking when talking”). A more detailed examination into cognitive functions showed that elderly fallers did less well than controls on executive function, attention, and motor skills, but performed similarly on information processing and memory functions [31]. Previous studies of cognitive-motor dual-task behaviors in elderly subjects with executive cognitive impairment have also shown a negative impact on postural control [4]. Clinical evidence suggests that postural stability in PD also deteriorates when performing multiple tasks at the same time, a requirement often encountered in daily activities. This is in keeping with a body of literature indicating that cognitive impairment, especially the limited ability of dual-tasking (e.g., “talking during walking”) has a negative impact on gait functions, such as increased stride variability, increasing the risk of falls [30, 83, 86]. Consequently, gait worsening during dual-task conditions (high dual-task gait cost) has been identified as a risk factor for the development of dementia [56].

It is clear that cognitive impairment is an important risk factor for falls. Higher-level motor control requires intact cognition to produce the complex motor responses in response to multi-modal sensory inputs and environmental challenges [53]. This is of particular importance as falls in cognitively impaired persons tend to occur more indoors and when distracted or multitasking during usual activities of daily living [73]. The presence of cognitive impairment may reduce the brain’s compensatory ability to ensure safe ambulation and prevent falls [34]. Cognition-enhancing pharmaceuticals (“cognitive enhancers”) may, therefore, be a suitable intervention to target risk factors and mitigate fall risk in the elderly.

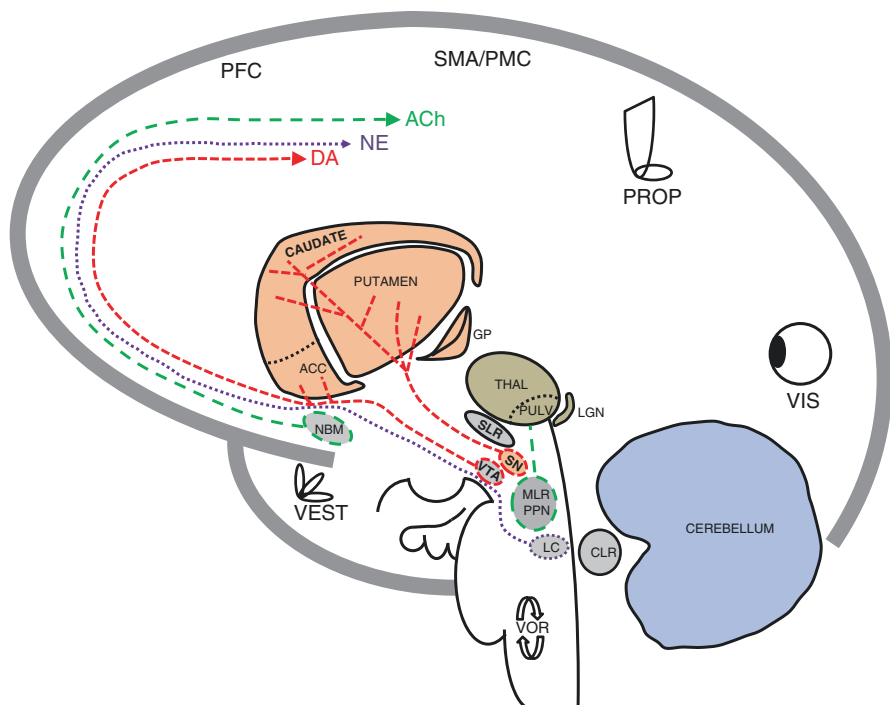
This chapter reviews recent studies of pharmacological cognitive enhancers and motor determinants of fall risk in the elderly.

---

## **Toward a Neurobiology of Falls: Cholinergic Brain Changes in PD Fallers**

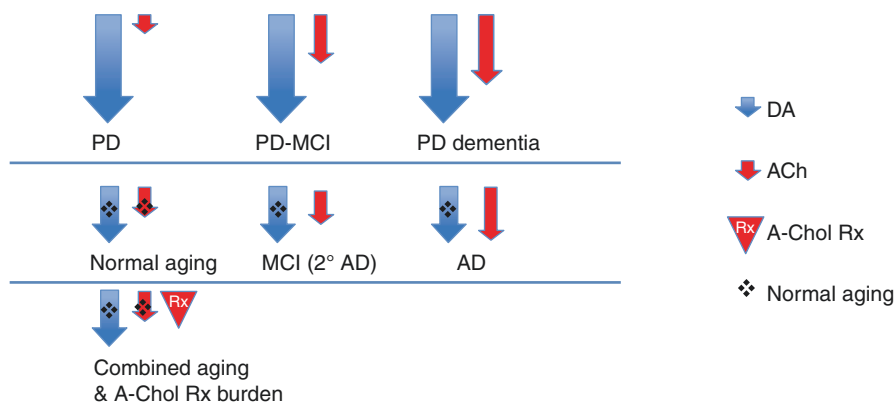
Falls are a major problem in older adults and neurodegenerative conditions alike. Parkinson disease (PD) is the second most common neurodegenerative disorder. A review of prospective studies showed that 61% of people with PD have at least a single fall in a year and 39% fall more often [3]. To compensate for gait slowing and instability walking becomes an attention-demanding task in order to prevent falls in patients with PD. However, even in early disease, executive dysfunction increased the demand on attentional processes [71]. Stability is particularly compromised during the execution of complex motor activities (e.g., turning) or while walking and performing concurrent tasks where demands on attention outweigh capacity. Consequently, gait becomes unstable and falls occur. Cognitive impairment as a risk factor for gait changes and falls also suggests the presence of a shared pathophysiology between cognitive and mobility functions. Axial motor impairments, including falls, have limited responsiveness to dopaminergic agents. Notably, studies have shown that the use of dopamine agonists and higher dosage of levodopa may actually increase fall risk in PD [3]. Therefore, mobility impairments probably arise from an intricate interplay of multi-system degenerations and neurotransmitter changes that extend beyond the loss of nigral dopaminergic neurons (Fig. 19.1). Unlike early stage PD where there is evidence of uniform and severe dopaminergic denervation, subcortical and cortical cholinergic denervation is more heterogeneous with some subjects have decreased and others preserved activity [17]. Cholinergic denervation has been associated with the presence of cognitive impairment and dementia in both PD and AD as shown in post-mortem and in vivo imaging studies [14, 79, 80]. The heterogeneity of subcortical cholinergic denervation may contribute to the variability of the motor phenotype in PD. For example, we showed previously that PD fallers did not differ in the degree of nigrostriatal dopaminergic denervation but had significantly decreased thalamic (likely reflecting pedunclopontine nucleus) and cortical cholinergic innervation compared to non-fallers [15]. Loss of thalamic cholinergic functions is likely to reflect pedunclopontine nucleus (PPN) neuron dysfunction or degeneration and is associated with abnormal sensory processing during postural control [58]. Animal studies have established that the dual loss of dopaminergic and cholinergic networks precipitates gait instability, freezing of gait and falls in PD [36, 39]. Therefore, cholinergic denervation may increase fall risk by impairing cortical cognitive function and/or abnormal sensory processing of postural functions [58]. Amelioration of this underlying cholinergic deficit with cholinergic drugs represents a promising strategy to target the etiology of falls in PD.

The incidence of falls in PD is only about two times higher than rates seen in community-dwelling elderly [11], suggesting that falls are frequent in both normal



**Fig. 19.1** Pictorial schematic of the neurochemical projections and key locomotor and sensory systems involved in the regulation of balance and gait. ACh Acetylcholine, ACC Nucleus Accumbens, CLR Cerebellar Locomotor Region, DA dopamine, GP Globus Pallidus, LC Locus Coeruleus, LGN Lateral Geniculate Nucleus, MLR Mesencephalic Locomotor Region, NBM Nucleus Basalis of Meynert, NE norepinephrine, PFC Prefrontal Cortex, PMC Primary Motor Cortex, PPN Pedunculopontine Nucleus, PROP Proprioception, PULV Pulvinar, SLR Subthalamic Region, SMA Supplementary Motor Area, SN Substantia Nigra, THAL Thalamus, VEST Vestibular, VIS Vision, VOR Vestibulo-Ocular Reflex, VTA Ventral Tegmental Area

aging and PD. Interestingly, PD—at least in terms of neurotransmitter changes—can be seen as accelerated normal aging (Fig. 19.2). First, normal aging is associated with significant loss of dopaminergic neuron nerve terminal function, about 5–8% per decade of adult life [13, 16, 78]. Although an average person may lose about 25–40% of striatal dopaminergic innervation between the ages of 25 and 75 years [78], this is not as severe as in PD where losses often exceed 50–80% [12]. It should be noted that normal aging is associated with notable inter-individual variability in dopaminergic changes with some elderly having more pronounced age-associated striatal dopaminergic denervation (AASDD) while others have less reductions [16, 82]. We have previously reported that AASDD plays a role in the etiology of multiple falls in older community-dwelling adults [16]. Second, normal aging is also associated with cholinergic losses but at a slower rate compared to the loss of striatal dopamine. For example, Kuhl et al. found a 3.7% loss of cholinergic



**Fig. 19.2** Commonalities in loss of dopaminergic and cholinergic neurotransmitter functions between PD and normal aging. Age-associated cholinergic losses likely increase cholinergic vulnerability in the elderly when exposed to anticholinergic medication burden

nerve terminals per decade of normal adult life [40]. However, additional exposure to anticholinergic medication drug burden at older age may tip the scale to clinical manifestations, including falls. Therefore, insights learned from the neurobiology of falls in PD may be applicable to normal aging as loss of dopaminergic and cholinergic functions occur in both conditions with only relative differences.

### Commonly Used Medications and Increased Fall Risk in the Elderly: The Emerging Recognition of Adverse Fall Risk of Anticholinergic Drug Burden

There are several classes of commonly used medications that significantly increase fall risk in the elderly. There is a consistent association between the use of most types of psychoactive drugs and falls in the elderly, including benzodiazepines, neuroleptics, and antidepressants (mainly tricyclic antidepressants), sedatives, and hypnotics [23, 42, 51, 65, 76]. Furthermore, the relative risk of traumatic falls of opioid use may be as large as for benzodiazepine use [47]. More recent studies highlight the importance of the unintended side effects of medications with anticholinergic properties. Prescription drugs given to elderly often have anticholinergic effects, as do many popular over-the-counter drugs [60]. Medications with anticholinergic properties could contribute to falls risk due to the anticholinergic effects on cognition, vision, or cause sedation [5]. A recent meta-analysis found that exposure to certain individual anticholinergic drugs or increased overall anticholinergic drug burden may increase the risk of falls, cognitive impairment, and all-cause mortality in older adults [69]. A case-control study of elderly psychiatric inpatients exemplified this, showing that anticholinergic medication burden was a more significant predictor of fall status than the use of benzodiazepine, antidepressants, or antipsychotics [1]. A prospective study found that elderly women using multiple

anticholinergic medications had a 100% increase in the risk of recurrent falls over a 1.5-year period and even anticholinergics likely to be used intermittently (such as antihistamines) increased the risk of recurrent falls [52]. This study also showed that there was a significant association between longer duration of anticholinergic use and recurrent falls. This observation could not be explained by specific subclasses of cholinergic medications as each of the anticholinergic subclasses was associated with fall recurrence [52]. These studies provide evidence that anticholinergic medication use is associated with increased risk for (recurrent) falls; however, provide no further insight into the underlying mechanism. Nebes et al. previously reported that elevated serum anticholinergic activity was associated with a significant slowing in simple response time and gait speed resulting in psychomotor slowing [60]. Similarly, a recent study found that the association between recurrent and injurious falls and increased anticholinergic medication burden was mediated through gait and balance impairments and could not be explained by muscular weakness [87]. There is also evidence that anticholinergic burden effects on mobility may be mediated through adverse effects of these drugs on cognition [18].

---

## **Cognitive Pharmacotherapy, Mobility Functions, and Fall Risk in PD and Other Neurodegenerative Disorders**

### **Studies in PD Fallers**

The relationship between cholinergic deficits and fall status in PD raises the question as to whether cholinergic pharmacotherapy may be useful as a strategy to reduce or prevent falls in this condition. Cognitive deficits of executive function and attention, risk factors for falls in PD, can be improved by cholinesterase inhibitor therapy [22]. Therefore, amelioration of underlying cholinergic deficiencies with cholinesterase inhibitors (donepezil, galantamine, rivastigmine) represents a promising strategy, targeting the etiology of falls in PD.

An open controlled trial of the use of galantamine at a maximum dose of 16 mg/day for 24 weeks included 41 subjects with PD dementia who were randomized to a galantamine treatment group (21 patients) versus a control group (20 patients) [44]. Improvements in falls and ratings of gait and freezing ( $p < 0.005$ ) were observed in the galantamine group compared to the control group.

Efficacy of cholinesterase inhibitor drugs has also been suggested in three phase 2 randomized placebo-controlled clinical trials [19, 33, 43] (Table 19.1). A small ( $n = 23$ ) cross-over trial reported that treatment with donepezil for 6 weeks reduced falls rates by 50% compared to placebo [19]. Frequently falling PD subjects (defined as falling or nearly falling more than 2 times per week) demonstrated the most improvement. Furthermore, a subset of patients who had deep brain stimulators appeared to respond as well as those treated medically. Donepezil treatment did not result in improvement performance on balance confidence scores or the Berg balance scale. One subject experienced worsening of tremor. Two patients with motor freezing behaviors did not appear to benefit from the drug.



**Table 19.1** Summary of controlled cholinesterase inhibitor clinical trials and falls in PD

Study	Drug and dosing	Class	Population	Design	Effect on falls
Litvinenko et al. [44]	Galantamine up to a maximum dose of 16 mg/day over 24 weeks	AChE inhibitor	PD with dementia ( <i>n</i> = 41)	Open-label controlled study	Improvements in falls (based on Unified PD Rating Scale measures) in the galantamine treatment group compared to the control group. The mean score for “falling” on the Unified PD Rating Scale decreased from $2.9 \pm 0.4$ to $2.3 \pm 0.3$ ( $p = 0.04$ ), that for “freezing” decreased from $3.0 \pm 0.5$ to $2.3 \pm 0.4$ ( $p = 0.03$ ), and the severity of gait impairment decreased from $3.1 \pm 0.4$ to $2.6 \pm 0.3$ ( $p = 0.04$ )
Chung et al. [19]	Donepezil, orally (5 mg 3 weeks, 10 mg 3 weeks)	AChE inhibitor	PD ( <i>n</i> = 23)	Double-blind placebo-controlled randomized cross-over trial	Fall frequency was reduced from 0.25 on placebo to 0.13 on treatment
Li et al. [43]	Rivastigmine, 3 mg twice daily for 52 weeks	AChE/BuChE inhibitor	PD-MCI ( <i>n</i> = 54) and PD dementia ( <i>n</i> = 35)	Randomized placebo-controlled trial	The number of falls (per person/years) was reduced from 4.26 on placebo to 1.82 on treatment
Henderson et al. [33]	Rivastigmine, 3–6 mg twice daily for 32 weeks	AChE/BuChE inhibitor	Non-demented PD fallers ( <i>n</i> = 130) randomized to rivastigmine v.s. placebo. Median fall rate was 0.5 and 1.14 per month in the rivastigmine and placebo group, respectively	Randomized placebo-controlled trial	The number of falls per month was reduced from 2.4 on placebo to 1.4. This reduction was attributed to improved step time variability and gait speed in simple and dual-task conditions along with improved balance. For example, step time variability was 28% lower ( $p = 0.002$ ) in the normal walking task and 21% lower (0.79, 0.62–0.99; $p = 0.045$ ) during the simple dual task in those assigned to rivastigmine compared with those assigned to placebo

Abbreviations: AChE acetylcholinesterase, BuChE butyrylcholinesterase

Li et al. performed a 12-month randomized, placebo-controlled, and double-blinded study. PD subjects were divided into a cognitive impairment group (PD-CI) and a normal cognition control group. Only the PD patients with cognitive impairment (either MCI or dementia;  $N = 81$ ) received adjuvant treatment with either a placebo or rivastigmine (single dose 3 mg two times daily). Confirming previous observations, the investigators found a gradient of increased fall frequency for cognitively normal PD patients to the cognitively most severely impaired PD patients (PDD). Within the cognitively impaired groups of PD patients, the investigators also found a reduced odds ratio of falling (0.31, 95% CI 0.12, 0.77,  $p < 0.01$ ) with 1 year of rivastigmine treatment compared to placebo [43].

Henderson et al. conducted a larger ( $n = 130$ ) single-center randomized clinical trial using rivastigmine in PD patients with a history of at least one fall in the past year [33]. Patients were treated with 32 weeks of rivastigmine which was uptitrated to a target dose of 12 mg per days over 16 weeks and then maintained at the highest tolerated dose for an additional 16 weeks. The primary endpoint was the difference in step time variability between the two groups at 32 weeks, adjusted for the number of falls in the previous year and baseline step time variability, cognition, and age. Step time gait variability was measured with a triaxial accelerometer during an 18 m walking task in three conditions: normal walking, simple and complex dual tasks. At week 32, those assigned to rivastigmine had improved step time variability for normal walking ( $p = 0.002$ ) and the simple dual task ( $p = 0.045$ ). Improvements in step time variability for the complex dual task did not differ between the two groups. Importantly, rivastigmine-treated patients in the study also had a lower fall frequency with a mean of 1.4 falls per month compared to 2.4 falls per month among patients treated with placebo (45% reduction). Statistically significant improvements in gait speed and balance were also observed. However, no significant improvement or changes were seen for the motor Unified Parkinson's Disease Rating Scale scores. It is possible that cholinergic system dysfunction is implicated in some more episodic or capacity processing-dependent components of postural instability and gait difficulties in PD, in particular falls, but not with overall trait severity of motor impairments.

These cholinesterase inhibitor trials in PD have demonstrated efficacy suggesting that cholinergic drugs may present a promising therapeutic potential to improve gait and balance and reduce the risk of falls in patients with PD.

## Studies in MCI and AD

A meta-analysis of the literature provided some evidence that anti-AD medications (acetylcholinesterase inhibitors and memantine) may improve some aspects of gait performance, providing a justification for clinical trials [10]. For example, the results of small open-label cholinesterase inhibitor trials in MCI and AD suggest that some elements of gait function may improve [6, 55]. Montero-Odasso et al. performed an open-label phase 2 clinical trial evaluating the effect of donepezil on gait in patients with mild AD ( $n = 43$ ) and found that subjects treated with donepezil

experienced statistically significant improvements in single- and dual-task gait velocity after 4 months of treatment [53] (Table 19.2). Changes in stride time variability did not achieve statistical significance. Cognitive improvements were seen in executive function tests (Trail Making Test).

These studies reported on biomechanical measures of fall risk, however, did not specifically assess fall risk. Hence, it is premature to advocate the use of cholinesterase inhibitors for the management of falls in this population. Moreover, caution is also in order as the use of anti-AD drugs has been reported to actually increase the risk of falls [24]. However, this retrospective report using data from Alzheimer's Disease Neuroimaging Initiative was not able to differentiate between falls and syncope. Cholinesterase inhibitors can cause syncope due to bradycardia and are contraindicated in those that risk of syncope. Similar paradoxical effects have been observed for the use of dopaminergic medications in PD [3]. Fall behaviors are complex and falls are more common with increasing physical activity, including improved ambulatory functions. Therefore, studies should employ outcome parameters that are not limited to fall frequency, often a stochastic event, but also health-related benefits and improved quality of life measures due to improved mobility functions.

**Table 19.2** Listing of cholinergic pharmacotherapy gait studies in MCI and AD subjects

Reference	Drug and dosing	Class	Population	Design	Clinical effects
Assal et al. [6]	Galantamine (24 weeks)	AChE inhibitor	Alzheimer disease ( $n = 9$ )	Open label	Improved stride time under dual-task condition with galantamine treatment
Montero-Odasso et al. [55]	Donepezil (5 mg for 1 month, and then 3 months with 10 mg/day) only in AD subjects. No treatment in the MCI control subjects	AChE inhibitor	Alzheimer disease ( $n = 6$ ); MCI control group ( $n = 9$ )	Open label	AD subjects had improved gait velocity after 1 month under single and dual tasking conditions. Gait variability decreased (improved) during follow-up. These increases were maintained for 4 months. Gait measures in the MCI group (no treatment) deteriorated
Montero-Odasso et al. [53]	Donepezil (5 mg/d for 1 mo and then 10 mg/d, open label for 3 months)	AChE inhibitor	Alzheimer disease ( $n = 43$ )	Open label	Donepezil improved gait in participants with mild AD. The enhancement of dual-task gait suggests the positive changes achieved in executive function as a possible causal mechanism

## Noradrenergic Drugs and Mobility in PD

Methylphenidate is a derivative of amphetamine that inhibits catecholamine reuptake, increasing norepinephrine and dopamine levels. The effects of methylphenidate on motor deficits have shown variable results. Early small, open-label pilot studies suggested that the drug may improve gait, and especially freezing, in patients with severe PD [9, 21, 64], which was not confirmed in other trials [8, 62]. A randomized, placebo-controlled, double-blind 6-month trial showed that methylphenidate in doses up to 80 mg per day did not improve gait [26]. However, a randomized clinical trial of methylphenidate in patients with PD who had undergone deep brain stimulation of the subthalamic nucleus found a benefit in the primary outcome parameter of the number of steps during a stand-walk-sit test without levodopa [57]. The authors concluded that methylphenidate improved gait hypokinesia and freezing, but only in those post-surgical patients with advanced PD. Notably, the number of patients with improved freezing of gait episodes in the on-levodopa condition was significantly higher in the catechol O-methyltransferase Val/Val subgroup compared to the catechol O-methyltransferase Met/Met genetic subgroup. However, no reduction in falls was seen with methylphenidate therapy. Results of dopamine transporter imaging in a subset of these patients demonstrated significant effects on striatal dopamine binding suggest at least a partial dopaminergic mechanism in this study [57]. Atomoxetine, a selective inhibitor of norepinephrine uptake, failed to demonstrate gait and postural benefits in PD [35].

Droxidopa, a prodrug of norepinephrine, has been recently approved for the short-term treatment of neurogenic orthostatic hypotension [37]. Droxidopa crosses the blood-brain barrier and is metabolized in the central nervous system to norepinephrine. While its primary function is as a central stimulator of sympathetic outflow it may also have cognitive effects due to its increase of endogenous norepinephrine [37]. A recent randomized, placebo-controlled, double-blinded clinical trial of droxidopa in PD patients with symptomatic neurogenic orthostatic hypotension showed a reduced fall rate in the droxidopa-treated group compared to the placebo group [32]. While these results are promising it is difficult to interpret whether effects can be primarily explained by improved orthostatic pressure or intrinsic noradrenergic cognitive benefits [32, 37] (Table 19.3).

---

## Discussion

### Cognitive Enhancer Therapy and Falls in PD

The neurobiology of falls, at least in terms of neurotransmitter changes, is best understood from studies in patients with PD. Converging *in vivo* imaging, post-mortem, and animal studies implicate an important role of the cholinergic system in the context of severe striatal dopaminergic denervation [15, 36, 39, 58]. These observations have been successfully translated into controlled clinical studies showing that cholinesterase inhibitors reduce fall frequency in PD [19, 33, 43]. Interestingly, both dopaminergic and cholinergic neurotransmitter change in PD

**Table 19.3** Summary of controlled noradrenergic clinical trials and gait or falls in PD

Study	Drug and dosing	Class	Population	Design	Effect on falls
Espay et al. [26]	Methylphenidate (maximum of 80 mg/days) for 60 days	Centrally active mixed norepinephrine and dopamine transporter inhibitor	PD with moderate gait impairment on high dose of levodopa ( $n = 17$ )	Double-blind, placebo-controlled study with a crossover design (12 weeks of treatment with 3 week wash-out)	Methylphenidate did not improve gait as assessed by the Freezing of Gait questionnaire, the freezing diary, and kinematic gait variables except for a slight improvement of the gait composite score in the “off” medication state. Further, parkinsonian motor function and depression tended to deteriorate in patients treated with methylphenidate. No benefits on falls were seen
Moreau et al. [57]	Methylphenidate up-titrated over 4 weeks to a maximum of 1 mg/kg per day (four to eight 10 mg capsules) divided into three doses (at 0800 h, 1200 h, and 1600 h). Dose lowering to 0.8 mg/kg was allowed as clinically indicated. Total duration of study was 90 days	Centrally active mixed norepinephrine and dopamine transporter inhibitor	Advanced PD with implanted subthalamic nucleus neurostimulators ( $n = 65$ randomized to methylphenidate vs. placebo)	Randomized controlled trial	The number of steps during a stand-walk-sit test and freezing motor behaviors without levodopa improved with methylphenidate treatment compared to placebo. However, there was no reduction in falls. Results of dopamine transporter imaging in a subset of patients demonstrated significant effects on striatal dopamine binding suggest at least a partial dopaminergic mechanism in this study
Hauser et al. [32]	Droxidopa (300–1800 mg/day) over 10 weeks	Norepinephrine prodrug designed to preferentially act peripherally	PD with symptomatic neurogenic orthostatic hypotension ( $n = 255$ randomized to droxidopa vs. placebo)	Phase 3, randomized, placebo-controlled, double-blind trial	The fall rate was 0.4 falls per patient-week in the droxidopa group and 1.05 falls per patient-week in the placebo group yielding a relative risk reduction of 77%. Fall-related injuries occurred in 16.7% of droxidopa-treated patients and 26.9% of placebo-treated patients. Statistical significance varied between different statistical methods for the same data. Presumed fall benefits likely come from sympathetic autonomic effects rather than central cognitive enhancer effects

and normal aging albeit with a different magnitude of change [13, 16, 40, 78]. Therefore, insights learned from the neurobiology of falls in PD may be applicable to normal aging in targeted individuals. As normal aging is also associated with cholinergic vulnerability, this may explain the increased sensitivity to anticholinergic drug burden in the elderly.

Data from noradrenergic drug clinical trials on gait are less consistent but suggest improved gait functions but only in advanced post-surgical PD subjects. Fall-reducing effects of droxidopa in PD have shown promise as well; however, it remains unclear whether these effects are likely relative to the drug's blood pressure effects rather than cognitive enhancer effects. The challenge of every clinical trial remains to identify those subjects that are likely to benefit most from pharmacotherapy of falls. In vivo imaging studies that determine the relationship between the regional distribution and degree of cholinergic brain changes may guide the choice of appropriate trial candidates, especially in candidates who already have a history of more frequent falls.

### **Avoidance of Anticholinergic Drugs that Have Central Nervous System Effects as a Fall Risk-Reducing Strategy in the Elderly**

There is increasing evidence that anticholinergic medication use is associated with increased risk for recurrent falls in the elderly [52]. A recent study found that greater anticholinergic drug burden was associated with executive function and memory deficits, more severe cortical brain atrophy and reduced temporal lobe cortical thickness, and more severe clinical decline in the elderly [66]. Anticholinergic drugs may not only have adverse cognitive effects but also cause more psychomotor slowing that increases fall risk [60]. Therefore, the use of drugs with central anticholinergic side effects in elderly people should be reviewed and discontinued when indicated [5]. Furthermore, public health efforts should provide greater education for community-dwelling elderly explaining the risk of using over-the-counter anticholinergics, such as first-generation antihistamines [52]. Use of anticholinergic drugs that do not cross the blood-brain barrier should be preferentially prescribed when there is a clinical indication for anticholinergic drugs.

### **Need for a more Harmonized Approach to Define Appropriate Outcome Measures for Pharmacological Studies Aimed at Reducing Fall Risk in the Elderly**

There are several challenges in treating falls. First, the etiology of falls is multifactorial and hence a single treatment intervention is unlikely to be effective. Second, the selection of the right treatment candidate will pose a challenge as well. For example, the evidence so far suggests that cognitive enhancer pharmacotherapy to reduce falls in the elderly should be limited to persons with cognitive impairment who are at increased risk of falling. Thirdly, and perhaps the largest challenge, how do we determine when a treatment is effective? The multifactorial etiology of falls will require also a targeted

selection of appropriate primary outcome parameters underlying fall risk. Although the number of falls may be the preferred outcome parameter, this may have limited validity if the frequency of falls is low. Successful cholinergic studies in PD showed that relative effects were most prominent for frequent fallers [20]. Even within the clinical setting of PD high fall frequency is only present in a small subset of patients. Therefore, the number of falls as the primary outcome parameter may not be optimal for pharmacotherapy interventions in elderly persons with less frequent falls. Furthermore, fear of falling with increasing sedentary behavior after a more sporadic fall may spuriously “improve” fall incidence and bias study findings. Furthermore, successful treatment may also lead to improved ambulatory functions resulting in higher levels of physical activity, paradoxically increasing the risk of falling and the frequency of falls.

These challenges pose the dilemma to choose appropriate surrogate outcome measures underlying fall risk. Most studies have focused on biomechanical gait or postural control proxy measures of fall risk as more suitable markers of fall risk. Examples include gait speed or gait variability that can be obtained under single- or dual-task test conditions. These measures are often obtained in the laboratory setting in more “static” conditions that do not adequately reflect the many gait and postural challenges that can be encountered during activities of daily living. Clinical standardized assessments may be helpful for assessing gait and postural control in more challenging situations. Commonly used tasks include the Timed Up and Go test [63], the dynamic gait index [74] or its derived functional gait assessment scale [85], and the Mini-BESTest [27]. These scales measure walking performance during real-world conditions, such as turning heads, changing direction, maneuvering obstacles, slowing/speeding up, closing eyes, and walking backward. These scales also have cut-off scores in classifying fall risk in older adults and predicting unexplained falls in community-dwelling older adults [74, 85]. [27]. The advantage of the Mini-BESTest is that it also provides a cut-off score to predict recurrent fall status in PD [48]. Accelerometers or other sensors can be applied to sub-tests of these composite scales to allow improved quantitative assessments rather than the simplified sum of ordinal variable scores [49, 50, 70]. More recently the increased emphasis has been placed on the use of “wearables” to estimate real-life mobility functions, although routine pragmatic use at this point still seems to be lacking [28]. Further research is needed to determine which of these surrogate outcome measures of fall risk are best suited for clinical trials. It is likely that the selection of these measures may be tailored to the more specific deficits seen in the target study population. Ultimately, however, any intervention should have tangible health benefits and most importantly improve the quality of life for the patients.

## **Future Directions: Novel Pharmacotherapy Approaches**

Antagonism of the 5-HT<sub>6</sub> receptor is a novel mechanism of action that promotes the release of acetylcholine as well as other neurotransmitters thought to improve cognition and function. Incidental observations of a clinical trial using the 5-HT<sub>6</sub> receptor inhibitor idalopirdine in combination with donepezil in AD found a threefold lower incident of falls during the treatment period compared to the donepezil



control group [81]. However, this was not confirmed in a larger analysis [7]. Interactions between the 5-HT<sub>6</sub> receptor antagonist idalopirdine and donepezil on falls in a rat model of impaired cognitive control of complex movements suggested that during fall-prone moments this treatment may improve the speed and efficacy of re-instating forward movement after relatively short halting steps [38]. The clinical translation of this murine model means that, hypothetically, this treatment may reduce fall propensity in PD patients via maintaining sequences of planned movement in working memory and improving the vigor of executing such movements following short periods of freezing of gait.

Other substrates of the cholinergic system are being targeted as well. While cholinesterase inhibitors will augment synaptic acetylcholine levels in all brain regions and cholinergic circuits, it may also have negative consequences for the neurocircuitry. For example, high synaptic and extrasynaptic acetylcholine levels may lead to inhibition of presynaptic cholinergic signaling by stimulation of presynaptic muscarinic type 2 receptors and non-physiological and tonic stimulation of postsynaptic muscarinic and nicotinic receptors [29]. More directed alternative strategies would be selective targeting of nicotinic cholinergic receptors. Nicotinic receptor subtype-specific compounds are in clinical trials for various indications. Preliminary data in animal studies suggest that drugs that selectively stimulate  $\alpha 4\beta 2$  nicotinic receptors have good entry into the brain and may improve mobility functions in rats with dual cholinergic and dopaminergic lesions [39]. It is possible that  $\alpha 4\beta 2$  nicotinic cholinergic receptor compounds, such as varinicine, may also improve mobility functions in PD. Possible mechanisms of  $\alpha 4\beta 2$  nicotinic cholinergic receptor could include improvement of cortical receptor changes underlying executive and attentional functions [72] or more directly the stimulation of postural and gait subcortical motor circuitry [41]. Centrally active noradrenergic drugs deserve special attention as an investigational treatment strategy of elderly fallers with cognitive impairment.

Therapeutic progress in the field of falls in the elderly is critically needed but will require carefully designed clinical trials using validated outcome measures in a personalized medicine approach [54]. Examples of a personalized medicine approach are the use of cholinesterase inhibitors in patients with PD with more frequent falls or who have falls in the setting of known clinical indicators for hypocholinergic activity, such as the presence of dream enactment behavior, cognitive impairment, or slow gait speed [59].

**Acknowledgment** The presented research data from the authors' work was supported by grants from the NIH [P01 NS015655, RO1 NS070856, with additional support from P50 NS091856], Department of Veterans Affairs [I01 RX000317] and the Michael J. Fox Foundation.

**Human Rights** All reported studies/experiments with human subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

**Disclosure** No potential conflicts of interest relevant to this chapter were reported.

## References

1. Aizenberg D, Sigler M, Weizman A, Barak Y. Anticholinergic burden and the risk of falls among elderly psychiatric inpatients: a 4-year case-control study. *Int Psychogeriatr*. 2002;14:307–10.
2. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and prediction of falls in dementia: a prospective study in older people. *PLoS One*. 2009;4:e5521. <https://doi.org/10.1371/journal.pone.0005521>.
3. Allen NE, Schwarzel AK, Canning CG. Recurrent falls in Parkinson's disease: a systematic review. *Parkinsons Dis*. 2013;2013:906274. <https://doi.org/10.1155/2013/906274>.
4. Anand V, Buckley JG, Scally A, Elliott DB. Postural stability in the elderly during sensory perturbations and dual tasking: the influence of refractive blur. *Invest Ophthalmol Vis Sci*. 2003;44:2885–91.
5. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ*. 2006;332:455–9. <https://doi.org/10.1136/bmj.38740.439664.DE>.
6. Assal F, Allali G, Kressig RW, Herrmann FR, Beauchet O. Galantamine improves gait performance in patients with Alzheimer's disease. *J Am Geriatr Soc*. 2008;56:946–7. doi:JGS1657 [pii]. <https://doi.org/10.1111/j.1532-5415.2008.01657.x>.
7. Atri A, et al. Effect of idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer disease: three randomized clinical trials. *JAMA*. 2018;319:130–42. <https://doi.org/10.1001/jama.2017.20373>.
8. Auriel E, Hausdorff JM, Giladi N. Methylphenidate for the treatment of Parkinson disease and other neurological disorders. *Clin Neuropharmacol*. 2009;32:75–81. <https://doi.org/10.1097/WNF.0B013E318170576C..00002826-200903000-00004> [pii].
9. Auriel E, Hausdorff JM, Herman T, Simon ES, Giladi N. Effects of methylphenidate on cognitive function and gait in patients with Parkinson's disease: a pilot study. *Clin Neuropharmacol*. 2006;29:15–7.
10. Beauchet O, Launay CP, Montero-Odasso M, Annweiler C, Allali G. Anti-dementia drugs-related changes in gait performance while single and dual tasking in patients with Alzheimer disease: a meta-analysis. *Curr Alzheimer Res*. 2015;12:761–71.
11. Beaulieu ML, Muller M, Bohnen NI. Have we been overestimating fall rates in Parkinson's disease? *Mov Disord*. 2017;32:803. <https://doi.org/10.1002/mds.26994>.
12. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J Neurol Sci*. 1973;20:415–55.
13. Bohnen NI, Albin RL, Koeppe RA, Wernette KA, Kilbourn MR, Minoshima S, Frey KA. Positron emission tomography of monoaminergic vesicular binding in aging and Parkinson disease. *J Cereb Blood Flow Metab*. 2006;26:1198–212.
14. Bohnen NI, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. *Arch Neurol*. 2003;60:1745–8. <https://doi.org/10.1001/archneur.60.12.1745>.
15. Bohnen NI, Muller ML, Koeppe RA, Studenski SA, Kilbourn MA, Frey KA, Albin RL. History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology*. 2009a;73:1670–6. doi:73/20/1670 [pii]. <https://doi.org/10.1212/WNL.0b013e3181c1ded6>.
16. Bohnen NI, Muller ML, Kuwabara H, Cham R, Constantine GM, Studenski SA. Age-associated striatal dopaminergic denervation and falls in community-dwelling subjects. *J Rehabil Res Dev*. 2009b;46:1045–52.
17. Bohnen NI, et al. Heterogeneity of cholinergic denervation in Parkinson's disease without dementia. *J Cereb Blood Flow Metab*. 2012;32:1609–17. <https://doi.org/10.1038/jcbfm.2012.60>.
18. Cao YJ, et al. Physical and cognitive performance and burden of anticholinergics, sedatives, and ACE inhibitors in older women. *Clin Pharmacol Ther*. 2008;83:422–9. <https://doi.org/10.1038/sj.clpt.6100303>.

19. Chung KA, Lobb BM, Nutt JG, Horak F. Cholinergic augmentation in frequently fallings subjects with Parkinson's disease. *Mov Disord.* 2009;24(Suppl 1):S259.
20. Chung KA, Lobb BM, Nutt JG, Horak FB. Effects of a central cholinesterase inhibitor on reducing falls in Parkinson disease. *Neurology.* 2010;75:1263–9. doi:WNL.0b013e3181f6128c [pii]. <https://doi.org/10.1212/WNL.0b013e3181f6128c>.
21. Devos D, et al. Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2007;78:470–5.
22. Dubois B, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. *Mov Disord.* 2012;27:1230–8. <https://doi.org/10.1002/mds.25098>.
23. Ensrud KE, et al. Central nervous system-active medications and risk for falls in older women. *J Am Geriatr Soc.* 2002;50:1629–37.
24. Epstein NU, Guo R, Farlow MR, Singh JP, Fisher M. Medication for Alzheimer's disease and associated fall hazard: a retrospective cohort study from the Alzheimer's Disease Neuroimaging Initiative. *Drugs Aging.* 2014;31:125–9. <https://doi.org/10.1007/s40266-013-0143-3>.
25. Eriksson S, Gustafson Y, Lundin-Olsson L. Risk factors for falls in people with and without a diagnose of dementia living in residential care facilities: a prospective study. *Arch Gerontol Geriatr.* 2008;46:293–306. <https://doi.org/10.1016/j.archger.2007.05.002>.
26. Espay AJ, et al. Methylphenidate for gait impairment in Parkinson disease: a randomized clinical trial. *Neurology.* 2011;76:1256–62. <https://doi.org/10.1212/WNL.0b013e3182143537>.
27. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med.* 2010;42:323–31. <https://doi.org/10.2340/16501977-0537>.
28. Godfrey A. Wearables for independent living in older adults: gait and falls. *Maturitas.* 2017;100:16–26. <https://doi.org/10.1016/j.maturitas.2017.03.317>.
29. Hasselmo ME, Sarter M. Modes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology.* 2011;36:52–73. doi:npp2010104 [pii]. <https://doi.org/10.1038/npp.2010.104>.
30. Hausdorff JM, Balash J, Giladi N. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. *J Geriatr Psychiatry Neurol.* 2003;16:53–8.
31. Hausdorff JM, Doniger GM, Springer S, Yogev G, Giladi N, Simon ES. A common cognitive profile in elderly fallers and in patients with Parkinson's disease: the prominence of impaired executive function and attention. *Exp Aging Res.* 2006;32:411–29.
32. Hauser RA, Heritier S, Rowse GJ, Hewitt LA, Isaacson SH. Droxidopa and reduced falls in a trial of Parkinson disease patients with neurogenic orthostatic hypotension. *Clin Neuropharmacol.* 2016;39:220–6. <https://doi.org/10.1097/WNF.0000000000000168>.
33. Henderson EJ, et al. Rivastigmine for gait stability in patients with Parkinson's disease (ReSPonD): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016; [https://doi.org/10.1016/S1474-4422\(15\)00389-0](https://doi.org/10.1016/S1474-4422(15)00389-0).
34. Herman T, Mirelman A, Giladi N, Schweiger A, Hausdorff JM. Executive control deficits as a prodrome to falls in healthy older adults: a prospective study linking thinking, walking, and falling. *J Gerontol A Biol Sci Med Sci.* 2010;65:1086–92. <https://doi.org/10.1093/gerona/glq077>.
35. Jankovic J. Atomoxetine for freezing of gait in Parkinson disease. *J Neurol Sci.* 2009;284:177–8. doi:S0022-510X(09)00508-5 [pii]. <https://doi.org/10.1016/j.jns.2009.03.022>.
36. Karachi C, et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. *J Clin Invest.* 2010;120:2745–54. <https://doi.org/10.1172/JCI42642>.
37. Kaufmann H, Norcliffe-Kaufmann L, Palma JA. Droxidopa in neurogenic orthostatic hypotension. *Expert Rev Cardiovasc Ther.* 2015;13:875–91. <https://doi.org/10.1586/14779072.2015.1057504>.
38. Kucinski A, de Jong IE, Sarter M. Reducing falls in Parkinson's disease: interactions between donepezil and the 5-HT6 receptor antagonist idalopirdine on falls in a rat model of impaired cognitive control of complex movements. *Eur J Neurosci.* 2017;45:217–31. <https://doi.org/10.1111/ejn.13354>.
39. Kucinski A, Paolone G, Bradshaw M, Albin RL, Sarter M. Modeling fall propensity in Parkinson's disease: deficits in the attentional control of complex movements in rats with

- cortical-cholinergic and striatal-dopaminergic deafferentation. *J Neurosci*. 2013;33:16522–39. <https://doi.org/10.1523/JNEUROSCI.2545-13.2013>. 33/42/16522 [pii]
40. Kuhl D, et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. *Ann Neurol*. 1996;40:399–410.
  41. Lambert CS, Philpot RM, Engberg ME, Johns BE, Wecker L. Analysis of gait in rats with olivocerebellar lesions and ability of the nicotinic acetylcholine receptor agonist varenicline to attenuate impairments. *Behav Brain Res*. 2015;291:342–50. <https://doi.org/10.1016/j.bbr.2015.05.056>.
  42. Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc*. 1999;47:30–9.
  43. Li Z, Yu Z, Zhang J, Wang J, Sun C, Wang P, Zhang J. Impact of rivastigmine on cognitive dysfunction and falling in Parkinson's disease. *Patients Eur Neurol*. 2015;74:86–91. <https://doi.org/10.1159/000438824>.
  44. Litvinenko IV, Odinak MM, Mogil'naya VI, Emelin AY. Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). *Neurosci Behav Physiol*. 2008;38:937–45. <https://doi.org/10.1007/s11055-008-9077-3>.
  45. Lundin-Olsson L, Nyberg L, Gustafson Y. 'Stops walking when talking' as a predictor of falls in elderly people. *Lancet*. 1997;349:617.
  46. Luukinen H, Koski K, Laippala P, Kivela SL. Predictors for recurrent falls among the home-dwelling elderly. *Scand J Prim Health Care*. 1995;13:294–9.
  47. Machado-Duque ME, Castano-Montoya JP, Medina-Morales DA, Castro-Rodriguez A, Gonzalez-Montoya A, Machado-Alba JE. Association between the use of benzodiazepines and opioids with the risk of falls and hip fractures in older adults. *Int Psychogeriatr*. 2017;1–6. <https://doi.org/10.1017/S1041610217002745>.
  48. Mak MK, Auyeung MM. The mini-BESTest can predict parkinsonian recurrent fallers: a 6-month prospective study. *J Rehabil Med*. 2013;45:565–71. <https://doi.org/10.2340/16501977-1144>.
  49. Mancini M, Fling BW, Gendreau A, Lapidus J, Horak FB, Chung K, Nutt JG. Effect of augmenting cholinergic function on gait and balance. *BMC Neurol*. 2015;15:264. <https://doi.org/10.1186/s12883-015-0523-x>.
  50. Mancini M, Salarian A, Carlson-Kuhta P, Zampieri C, King L, Chiari L, Horak FB. ISway: a sensitive, valid and reliable measure of postural control. *J Neuroeng Rehabil*. 2012;9:59. <https://doi.org/10.1186/1743-0003-9-59>.
  51. Marcum ZA, et al. Antidepressant use and recurrent falls in community-dwelling older adults: findings from the health ABC study. *Ann Pharmacother*. 2016a;50:525–33. <https://doi.org/10.1177/1060028016644466>.
  52. Marcum ZA, et al. Anticholinergic medication use and falls in postmenopausal women: findings from the women's health initiative cohort study. *BMC Geriatr*. 2016b;16:76. <https://doi.org/10.1186/s12877-016-0251-0>.
  53. Montero-Odasso M, et al. Donepezil improves gait performance in older adults with mild Alzheimer's disease: a phase II clinical trial. *J Alzheimers Dis*. 2015;43:193–9. <https://doi.org/10.3233/JAD-140759>.
  54. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: implications for risk assessment and prevention. *J Am Geriatr Soc*. 2018;66:367–75. <https://doi.org/10.1111/jgs.15219>.
  55. Montero-Odasso M, Wells J, Borrie M. Can cognitive enhancers reduce the risk of falls in people with dementia? An open-label study with controls. *J Am Geriatr Soc*. 2009;57:359–60. doi:JGS2085 [pii]. <https://doi.org/10.1111/j.1532-5415.2009.02085.x>.
  56. Montero-Odasso MM, et al. Association of dual-task gait with incident dementia in mild cognitive impairment: results from the gait and brain study. *JAMA Neurol*. 2017;74:857–65. <https://doi.org/10.1001/jamaneurol.2017.0643>.
  57. Moreau C, et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. *Lancet Neurol*. 2012;11:589–96. [https://doi.org/10.1016/S1474-4422\(12\)70106-0](https://doi.org/10.1016/S1474-4422(12)70106-0). S1474-4422(12)70106-0 [pii]

58. Muller ML, Albin RL, Kotagal V, Koeppel RA, Scott PJ, Frey KA, Bohnen NI. Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease. *Brain*. 2013;136:3282–9. <https://doi.org/10.1093/brain/awt247>. awt247 [pii]
59. Muller ML, Bohnen NI, Kotagal V, Scott PJ, Koeppel RA, Frey KA, Albin RL. Clinical markers for identifying cholinergic deficits in Parkinson's disease. *Mov Disord*. 2015;30:269–73. <https://doi.org/10.1002/mds.26061>.
60. Nebes RD, Pollock BG, Halligan EM, Kirshner MA, Houck PR. Serum anticholinergic activity and motor performance in elderly persons. *J Gerontol A Biol Sci Med Sci*. 2007;62:83–5.
61. Nevitt MC. Falls in the elderly: risk factors and prevention. In: Masdeu JC, Sudarsky L, Wolfson L, editors. *Gait disorders of aging*. Philadelphia: Lippincott–Raven; 1997.
62. Nutt JG, Carter JH, Carlson NE. Effects of methylphenidate on response to oral levodopa: a double-blind clinical trial. *Arch Neurol*. 2007;64:319–23. doi:64/3/319 [pii]. <https://doi.org/10.1001/archneur.64.3.319>.
63. Podsiadlo D, Richardson S. The timed “up & go”: a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39:142–8.
64. Pollak L, Dobronevsky Y, Prohorov T, Bahunker S, Rabey JM. Low dose methylphenidate improves freezing in advanced Parkinson's disease during off-state. *J Neural Transm Suppl*. 2007;72:145–8.
65. Ray WA, Thapa PB, Gideon P. Benzodiazepines and the risk of falls in nursing home residents. *J Am Geriatr Soc*. 2000;48:682–5.
66. Risacher SL, et al. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol*. 2016;73:721–32. <https://doi.org/10.1001/jamaneurol.2016.0580>.
67. Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. *Ann Intern Med*. 1994;121:442–51.
68. Rubenstein LZ, Powers CM, MacLean CH. Quality indicators for the management and prevention of falls and mobility problems in vulnerable elders. *Ann Intern Med*. 2001;135:683–93.
69. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: a systematic review and meta-analysis. *Br J Clin Pharmacol*. 2015;80:209–20. <https://doi.org/10.1111/bcp.12617>.
70. Salarian A, Horak FB, Zampieri C, Carlson-Kuhta P, Nutt JG, Aminian K. iTUG, a sensitive and reliable measure of mobility. *IEEE Trans Neural Syst Rehabil Eng*. 2010;18:303–10. <https://doi.org/10.1109/TNSRE.2010.2047606>.
71. Sarter M, Albin RL, Kucinski A, Lustig C. Where attention falls: increased risk of falls from the converging impact of cortical cholinergic and midbrain dopamine loss on striatal function. *Exp Neurol*. 2014;257C:120–9. <https://doi.org/10.1016/j.expneurol.2014.04.032>.
72. Sarter M, Parikh V, Howe WM. nAChR agonist-induced cognition enhancement: integration of cognitive and neuronal mechanisms. *Biochem Pharmacol*. 2009;78:658–67. doi:S0006-2952(09)00305-0 [pii]. <https://doi.org/10.1016/j.bcp.2009.04.019>.
73. Shaw FE. Falls in cognitive impairment and dementia. *Clin Geriatr Med*. 2002;18:159–73.
74. Shumway-Cook A, Woollacott MH. *Motor control: theory and practical applications*. Baltimore: Lippincott Williams & Wilkins; 1995.
75. Studenski S, Duncan PW, Chandler J. Postural responses and effector factors in persons with unexplained falls: results and methodologic issues. *J Am Geriatr Soc*. 1991;39:229–34.
76. Thapa PB, Gideon P, Cost TW, Milam AB, Ray WA. Antidepressants and the risk of falls among nursing home residents. *N Engl J Med*. 1998;339:875–82. <https://doi.org/10.1056/NEJM199809243391303>.
77. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med*. 1988;319:1701–7.
78. Volkow ND, et al. Dopamine transporters decrease with age in healthy subjects. *J Nucl Med*. 1996;37:554–8.
79. Whitehouse PJ, Martino AM, Wagster MV, Price DL, Mayeux R, Atack JR, Kellar KJ. Reductions in [<sup>3</sup>H]nicotinic acetylcholine binding in Alzheimer's disease and Parkinson's disease: an autoradiographic study. *Neurology*. 1988;38:720–3.

80. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR. Alzheimer's disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol.* 1981;10:122–6.
81. Wilkinson D, Windfeld K, Colding-Jorgensen E. Safety and efficacy of idalopirdine, a 5-HT<sub>6</sub> receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol.* 2014;13:1092–9. [https://doi.org/10.1016/S1474-4422\(14\)70198-X](https://doi.org/10.1016/S1474-4422(14)70198-X).
82. Wong KK, Muller ML, Kuwabara H, Studenski SA, Bohnen NI. Olfactory loss and nigrostriatal dopaminergic denervation in the elderly. *Neurosci Lett.* 2010;484:163–7. doi:S0304-3940(10)01083-9 [pii]. <https://doi.org/10.1016/j.neulet.2010.08.037>.
83. Wood BH, Bilclough JA, Bowron A, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry.* 2002;72:721–5.
84. Woollacott MH, Shumway-Cook A, Nashner LM. Aging and posture control: changes in sensory organization and muscular coordination. *Int J Aging Hum Dev.* 1986;23:97–114.
85. Wrisley DM, Marchetti GF, Kuharsky DK, Whitney SL. Reliability, internal consistency, and validity of data obtained with the functional gait assessment. *Phys Ther.* 2004;84:906–18.
86. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord.* 2008;23:329–42.
87. Zia A, Kamaruzzaman S, Myint PK, Tan MP. Anticholinergic burden is associated with recurrent and injurious falls in older individuals. *Maturitas.* 2016;84:32–7. <https://doi.org/10.1016/j.maturitas.2015.10.009>.



# Dual-Task Training in Cognitively Impaired and Intact Older Populations to Reduce Fall Risk: Evidence from Previous Intervention Trials by Using a Systematic Review Approach

# 20

Klaus Hauer, Phoebe Ullrich, and Christian Werner

## Introduction

Motor and cognitive performances are highly associated [1–3], and both the motor and cognitive status represent high-impact factors for clinically relevant adverse events such as risk of falls in older persons [4, 5]. Specific cognitive deficits have been identified which may represent the missing link between the extraordinary high risk of falling and the cognitive status in patients with and without cognitive impairment, as has been reviewed in previous chapter of Sect. I (Fundamentals) of this book [6–10].

Among cognitive candidates for a high association to risk of falling with a high potential to be used in an interventional approach, the ability to perform different tasks simultaneously (dual-task, DT) stands out. Significant associations of dual-task deficits to risk of falling have been identified in persons with cognitive impairment [11, 12] and in vulnerable populations, at high-risk for falls with a high prevalence of cognitive as well as motor impairment, such as nursing home residents [13]. DT performances are associated with aging and cognitive impairment when tested for basic motor domains such as strength and balance as part of the simultaneous tasks [14, 15]. Deficits in these motor domains already represent major risk factors for falls [4], while additional cognitive tasks additionally affect the already existing deficits in frail older persons with and without cognitive impairment [14, 15]. It is these key motor skills such as walking activities or sit-to-stand transfers that represent the hot spots of falling, indicating their high relevance with respect to risk exposure during physical activity in multimorbid persons such as nursing home residents [16].

---

K. Hauer (✉) · P. Ullrich · C. Werner  
Agaplesion Bethanien-Hospital/Geriatric Center at the Heidelberg University,  
Heidelberg, Germany  
e-mail: [khauer@bethanien-heidelberg.de](mailto:khauer@bethanien-heidelberg.de); [phoebe.koepp@bethanien-heidelberg.de](mailto:phoebe.koepp@bethanien-heidelberg.de);  
[christian.werner@bethanien-heidelberg.de](mailto:christian.werner@bethanien-heidelberg.de)



In the recent past, a large body of evidence has been accumulating that DT performances can be improved by specific training programs in different populations and settings suggesting generalizable benefits [17–19]. Although quite a number of these results have been achieved in highly specific and experimental studies focusing rather on the heuristic aspect to document associations of motor-cognitive performances [20–22] or the proof of concept with respect to trainability [23–25] in persons with and without cognitive impairment, it may now be the time to include those programs in rehabilitation and fall prevention.

To date, such a translation into clinical or rehabilitative programs seems largely limited and a systematic review of the state of art concerning the inclusion of DT strategies in fall prevention research is missing. A severe limitation to identifying all relevant studies may lie in the heterogeneity of study designs with respect to comprehensiveness of the DT training approach. However, to evaluate to what extent the DT training has been included in previous fall prevention programs, the whole range of DT training approaches will have to be documented despite facing relevant restrictions to identify especially those with insufficient design.

The focus of this chapter and the objective of this umbrella review of systematic reviews is therefore to identify intervention trials with an adequate study design (randomized controlled trial [RCT]) aiming at preventing falls in older persons by including “any type of DT training” in their intervention to allow a comprehensive overview of the state of current research.

---

## Methods

The search strategy was restricted by the nature of target definition. The goal of the search was to identify “any type of DT training” without losing studies with insufficient information in titles, abstracts, mesh/key terms, or manuscript. In a large number of fall prevention studies, only a marginal description of the DT approach was given. Such studies would not be identified by an established search strategy. We therefore combined content-related and formal search strategies to obtain a most comprehensive picture of the state of art for programs in fall prevention research which included DTs. To allow feasibility of such a very laborious literature search, we anchored the search by high-quality, comprehensive, preferably ongoing reviews as a base of further extensive, specified search strategies.

*In a first step*, we conducted a comprehensive literature search of systematic reviews in PubMed using a rather open search strategy: (((fall\*[Title/Abstract]) AND (reduc\*[Title/Abstract] OR prevent\*[Title/Abstract]))) AND intervention\*[Title/Abstract]) AND review[Title/Abstract]].

*In a second step*, due to the large number of potential systematic review articles retrieved ( $n = 1136$ ), we focused on a content-related, rather than formal search strategy. To further narrow the search, we analyzed the most recent Cochrane reviews on fall prevention [26–28] to find out if DT studies are related to specific domains of single- or multicomponent fall prevention programs (e.g., environmental, pharmaceutical, exercise, cognitive-behavioral, knowledge/educational, disease-related,

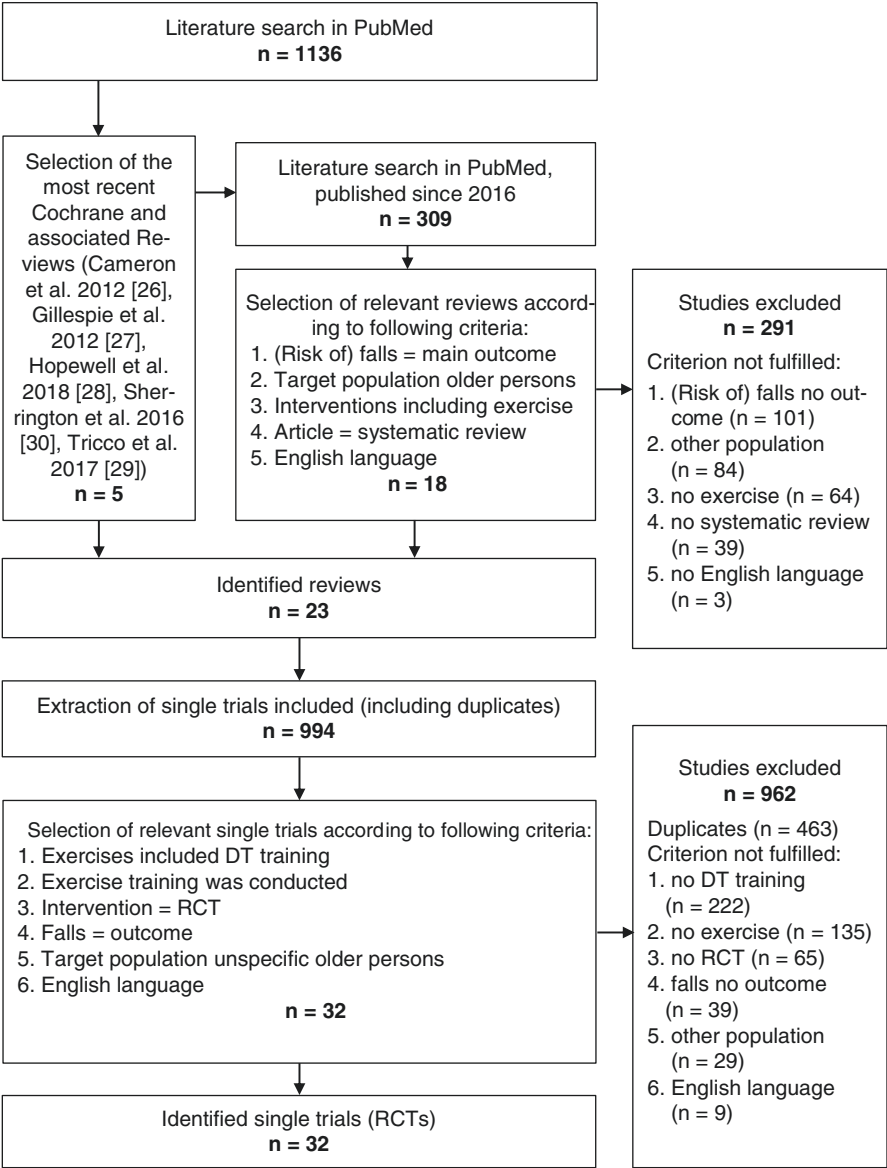
supportive device, and other interventions). The analysis documented that all potentially relevant DT interventions were allocated in the exercise domain only. The Cochrane reviews had been selected based on their high-quality search strategies and data analysis, the ongoing review process for Cochrane allowing an overview of articles published until the publication of the Cochrane reviews, and the comprehensive inclusion criteria for all domains of potentially relevant intervention strategies. To confirm the finding that potential DT articles were exclusively allocated to the exercise domain, we additionally screened a most recent, well-published, comprehensive fall prevention review [29] comparable to the Cochrane reviews to make sure not to have overlooked recent publications in other domains. Based on the confirmed finding that DT-related interventions had only been included in exercise-based trials, we then focused on exercise-related reviews for fall prevention in the final search.

*In a third step*, according to the abovementioned strategy and the high-quality Cochrane standards, we included another systematic review with focus on exercise-based fall prevention that was associated with the Cochrane Library [30], which we used as a base for exercise-associated fall prevention strategies and further focused on recent reviews including only papers which were published since 2016. Identified reviews were screened for eligibility by the title and abstract according to the following inclusion criteria:

1. Falls/risk of falls as main outcome criteria.
2. Target population = older persons (not specific subgroups such as persons living in specific regions, or persons with specific diseases, except for dementia-related diseases, representing a risk population most effected for specific attention-related deficits as addressed in DT training).
3. Interventional trials (RCTs) with single- or multicomponent interventions including exercises.
4. Article = systematic review.
5. English language.

*In a fourth step*, single studies as identified in all included basic reviews [26–30] and other identified systematic reviews, which met the above-listed inclusion criteria, were screened for eligibility by title, abstract and full text using the criteria 2, 3, and 5 as stated above for reviews with an additional 6th (“falls as a main outcome”) and seventh criterion (“DT exercises as part of the training program”). The results of the comprehensive search have been summarized in a flowchart (Fig. 20.1).

*In a final fifth step*, identified articles were analyzed and relevant information was extracted into a comprehensive table including the following variables: Author, year of publication; study design (study groups, intervention period, and observation period); sample characteristics (number, age, cognitive status); DT training; assessment (mobility, DT, falls) and status of assessment (primary or secondary end point), study results (effects on mobility, DT performance, and falls). Only results which were significant for the whole study group for between-group analyses according to a RCT design were included, excluding significant effects of subgroups and within-group analyses for IG/CG.



**Fig. 20.1** Flowchart of recruitment process

The table also includes a rating for the comprehensiveness and quality of the DT training approach used in the identified studies. For evaluating the heterogeneous DT approaches, we introduced four quality criteria for which we gave a dichotomous rating with (0) scoring for not achieved/insufficient information (negative scoring), or (1) for achieved (positive scoring). These quality criteria included the following:

1. Objective/background: Dual-tasking described as a study objective or at least as a focus in the introduction of the article (yes = 1 or no = 0).
2. Details of the DT training were sufficiently described (yes = 1 or no = 0).
3. DT assessment was implemented (yes = 1 or no = 0).
4. Effects on DT were described (yes = 1 or no = 0).

Finally, a score for the overall rating of the DT approach was calculated by summing up the ratings of the individual criteria (range 0–4) with higher scores indicating a DT approach of higher quality.

Identification of reviews and single articles were performed by two independent reviewers (EL, PU) and open issues were clarified by a third-party decision (KH). A competitive, complex formal search was undertaken leading to a substantially lower identification rate of adequate articles (data not shown) based on the difficulties as stated above, confirming the present search strategy.

---

## Results

### Literature Search

The formal search as described in methods as the first step yielded  $n = 1136$  hits for systematic reviews. The second step (content-related anchoring) included four high-quality reviews [26–29] confirming the search strategy to focus on exercise-related reviews only. In the third step, based on a high-quality review by Sherrington et al. 2016 [30],  $n = 309$  remaining reviews published since 2016 were screened based on predefined criteria. Main exclusion criteria were (descending relevance): (1) Falls/risk of falls with no main outcome criteria ( $n = 101$ ). (2) Target population not older persons (or specific subgroups such as persons with specific diseases, or persons living in specific regions; except for dementia-related diseases ( $n = 84$ )). (3) No inclusion of exercise in interventions ( $n = 64$ ). (4) Article no systematic review ( $n = 39$ ). (5) Article not in English language ( $n = 3$ ).

The final result comprised  $n = 23$  systematic reviews which met predefined criteria, also including the anchor reviews [6, 26–47]. Single articles reported in the reviews were then analyzed. After exclusion of duplicates ( $n = 463$ ),  $n = 531$  single articles remained. Out of these ( $n = 531$ ),  $n = 32$  articles were finally included in the present review [48–79] according to predefined inclusion criteria (see Fig. 20.1).

### Characteristics of Identified Articles

Extracted data on the identified articles were summarized in a comprehensive table according to variables which were relevant for the objective of this review (see Table 20.1).

**Table 20.1** Descriptive data analysis of identified articles

Author (year)	Study design	Sample	Assessment			Study results				DT quality rating			
			DT training	Mobility	DT	Falls	Mobility	DT			DT = objective	DT training details	DT assessment
								1st task	2nd task	Falls			
Ansai et al. (2016)	2 IG versus CG (UC) IP = 16 w. OP = 22 w.	$n = 69$ Age: $82 \pm 2$ y. COG <sup>a</sup> : Mix	IG 1: Walking and motor/ cognitive tasks	5STS, one-leg-stand, tandem (PO)	TUG and motor task (carrying cup of water; val.; PO)	$n$ of fallers (unsp.)	– (n.s.)	– (TUG time n.s.)	– (water loss n.s.)	– (n.s.)	0	0	1
Eggenberger et al. (2015)	2 IG versus CG (act) IP = 26 w. OP = 52 w.	$n = 89$ Age: $77 \pm 6$ – $81 \pm 5$ y. COG: NCI	IG1: Motor and cognitive task (exergame) IG2: Walking and cognitive task (memorizing words)	Walking (GAITRite) (PO); SPPB (extended), endurance (SO)	Walking (GAITRite) and cognitive task (counting, numerating) (PO)	$n$ of falls (SO)	+/- (+ step time fast walking; $p = 0.007$ ; – other: n.s.)	+ (step time variability at fast walking; DT costs: $p = 0.044$ )	Not given	– (n.s.)	1	1	1
Faber et al. (2006)	2 IG versus CG (UC) IP = 20 w. OP = 72 w.	$n = 278$ Age: $85 \pm 6$ y. COG: Mix	IG1: Walking and motor task (carrying)	POMA, PPS (SO)	n.a.	$n$ of falls, fallers, fall incidence (PO)	+/- (+ POMA: $p < 0.01$ ; – PPS n.s.)	n.a.	– n.a.	– (n.s.)	0	1	0
Gawler et al. (2016)	2 IG versus CG (UC) IP = 24 w. OP = 48 w.	$n = 1256$ Age: 73 y. COG: Mix	IG2: Walking and motor/ cognitive task (clapping every five steps, looking in different directions)	Funct. Reach, TUG (SO)	n.a.	$n$ of falls, fallers, $n$ of injurious falls (SO)	– (n.s.)	n.a.	– n.a.	– +/- (+ $n$ of injurious falls in IG2 versus CG $p = 0.04$ , $n$ of falls n.s.; $n$ of falls follow-up: + $p = 0.04$ )	0	1	0

Gianoudis et al. (2014)	IG versus CG (educ.) IP/OP = 52 w. $n = 162$ Age: $68 \pm 7$ (IG), $67 \pm 6$ (CG) y. COG: ?	IG: Balance and motor/ cognitive task	Muscle strength, stair climbing, STS, 4 square step test (PO)	TUG and cognitive task (counting, PO)	$n$ of falls (SO)	+/- (+ muscle strength, stair climbing, STS, 4 square step test: $p < 0.05$ )	– (TUG time n.s.)	– (n.s.)	0	0	1	1	2
Gschwind et al. (2015)	IG versus CG (educ.) IP = 16 w. OP = 24 w. $n = 153$ Age: $75 \pm 7$ (IG), $75 \pm 6$ (CG) y. COG: Mix	IG: Walking/ stepping and cognitive tasks (semantic and working memory, e.g., remembering objects)	PPA (PO), SPPB, TUG, walking speed, balance, 5STS, val; stepping (SO)	Walking and cognitive task (counting; balance, 5STS, val; SO)	$n$ of falls (unsp.)	+/- (+ PPA: $p = 0.035$ ; – other: n.s.)	+ (walking time: $p = 0.040$ )	Not given	1	1	1	1	4
Halvarsson et al. (2013)	IG versus CG (UC) IP = 12 w. OP = 78 w. $n = 59$ Age: $76$ (IG), $78$ (CG) y. COG: NCI	IG: Walking and motor/ cognitive tasks (counting, reading, carrying)	Habitual/fast gait (GAITrite), step execution (StepEx) (PO)	Step execution and cognitive task (reciting letters; non-val; PO)	$n$ of falls (SO)	+/- (+ fast) gait speed, cadence; $p < 0.05$ ; – other: n.s.)	+ (step execution time: $p = 0.039$ )	Not given	1	1	1	1	4
Helbostad et al. (2004)	IG versus CG (act) IP = 12 w. OP = 52 w. $n = 77$ Age: $81 \pm 5$ y. COG: Mix	IG: Balance/ walking & motor/ cognitive tasks (perceptual, cognitive, motor, mechanical manipulations)	Walking speed, walk + change direction, STS TUG, max. Step length, timed pick-up (PO), muscle strength, posturography, postural sway (SO)	Balance and cognitive task fall event (remembering rate, time to first fall non-val; SO) (unsp.)	$n$ of falls, fall event	– (n.s.)	– (n.s.)	Not given	0	1	1	1	3

(continued)





Ng et al. (2015)	4 IG versus CG (UC) IP = 26 w. OP = 52 w.	$n = 246$ Age: 70 y. COG: Mix	IG3/4: Balance and walking and motor/ cognitive tasks (carrying, talking, counting, calculating)	Walking speed, muscle strength (PO)	n.a.	n.a.	– (n.s.)	0	1	0	0	1
Nitz et al. (2004)	IG versus CG (act) IP = 10 w. OP = 13 w.	$n = 73$ Age: 76 ± 8 (IG), 76 ± 8 (CG) y. COG: ?	IG: Sit-to-stand/ ball games and motor/ cognitive tasks (e.g., nominating animals starting with a specific letter)	COVS, balance (func), muscle strength (PO), TUG Step, TUG cognitive tasks (unsp.)	– (n.s.)	Not given	– (n.s.)	1	1	1	1	4
Patil et al. (2015)	2 IG versus 2 CG (UC); (1 IG, 1 CG + Vit D) IP/OP = 104 w.	$n = 409$ Age: 74 ± 3 (IG), 74 ± 3 (CG) y. COG: NCI	IG1/2: Balance/ agility and motor/ cognitive? Tasks	Muscle strength, SPPB, walking speed, TUG, dynamic balance (unsp.)	n.a.	n.a.	– (n.s.)	0	0	0	0	0
Pitkälä et al. (2013)	2 IG versus CG (UC) IP/OP = 52 w.	$n = 210$ Age: 78 ± 5 y. COG: CI	IG1: Ball games/ manual motor task and cognitive task (counting)	FIM, SPPB	n.a.	n.a.	– (n.s.)	0	1	0	0	1

(continued)

Table 20.1 (continued)

Author (year)	Study design	Sample	DT training	Assessment			Study results			DT quality rating				
				Mobility	DT	Falls	Mobility	DT		DT = objective details	DT training assessment	Effects on DT	Overall rating <sup>a</sup>	
								1st task	2nd task					Falls
Schöne et al. (2015)	IG versus CG (educ.) IP = 16 w. OP = 26 w.	$n = 90$ Age: $82 \pm 7$ y, and cognitive tasks COG: NCI e.g., connecting numbers/ letters)	IG: Stepping tasks (part. Val., SO)	n.a.	TUG and cognitive task (SO)	$n$ of falls (SO)	n.a.	+ (time: $p = 0.030$ )	Not given	1	1	1	4	
Shigematsu et al. (2008)	IG versus CG (act) IP = 12 w. OP = 48 w.	$n = 68$ Age: $69 \pm 3$ y and cognitive task (provided step pattern) COG: ?	IG: Walking task (provided step pattern)	STS/30 sec, leg extension, single leg stand, funct. Reach, tandem walking, lying-standing up, reaction time, stepping, jumping, walking (unsp.)	Stepping in different directions after signal (non-val., unsp.) – Unclear, if assessment included DT	$n$ of falls (unsp.)	+/- (+ leg extension, tandem walking, stepping, walking, reaction time: $p < 0.05$ ; – other: n.s.)	+ (time $p < 0.001$ ), if DT assessment	Not given	0	1	0	1	
Siegrist et al. (2016)	IG versus CG (UC) IP = 16 w. OP = 52 w.	$n = 378$ Age: $78 \pm 6$ y, and motor/ cognitive tasks COG: ?	IG: Walking and motor/ cognitive tasks	TUG, STS, balance (mod. Romberg) (SO)	n.a.	$n$ of falls (PO), $n$ of fallers, $n$ of fall-related injuries (SO)	+/- (+ TUG, balance: $p < 0.05$ ; – STS n.s.)	n.a.	n.a.	0	0	0	0	
Sihvonon et al. (2004)	IG versus CG (unclear) IP = 4 w. OP = 52 w.	$n = 27$ Age: $81 \pm 6$ (IG), $83 \pm 4$ (CG) y. COG: ?	IG: Balance/ stepping and motor/ cognitive tasks	Balance (force platform), BBS (unsp.)	Incidence of falls, $n$ of injurious falls (PO)	Incidence of falls, $n$ of injurious falls (PO)	+ ( $p < 0.05$ )	n.a.	n.a.	0	0	0	0	

Skelton et al. (2005)	IG versus CG (act) IP = 36 w. OP = 50 w.	$n = 81$ Age: $73 \pm 6$ y. and motor/ COG: Mix	IG: Walking cognitive tasks (gaze or head movements, talking, clapping/5 steps)	n.a.	n.a.	n of falls, n of fall-related injuries(PO)	n.a.	n.a.	+/(n of falls $p = 0.029$ , other n.s.)	0	1	0	0	0	1
Smulders et al. (2010)	IG versus CG (UC) IP = 5.5 w. OP = 52 w.	$n = 96$ Age: $71 \pm 5$ y. and motor/ COG: ?	IG: Walking cognitive tasks (SO) carrying, counting a specific sound in a song)	Short ABC, activity level (SO)	n.a.	n of falls (PO)	+/(+ short ABC; $p = 0.038$ ; – activity level n.s.)	n.a.	+ ( $p < 0.05$ )	0	1	0	0	0	1
Swanenburg et al. (2007)	IG versus CG (educ.), IP = 13 w. OP = 52 w.	$n = 24$ Age: $71 \pm 7$ y. task and COG: ?	IG: Balance cognitive task (distraction)	BBS, postural balance (force platform) (PO), activity level, muscle strength (SO)	n.a.	n of falls (SO)	+/(+ BBS, activity level, muscle strength $p < 0.05$ ; – postural balance n.s.)	n.a.	– ?(no p-value given)	1	0	0	0	0	1
Treacy et al. (2015)	IG versus CG (UC) IP = 2 w. OP = 13 w.	$n = 162$ Age: $83 \pm 7$ (IG), $81 \pm 8$ (CG) y. COG: Mix	IG: Balance and motor task (throwing, catching a ball)	SPPB balance + one-leg- stand (PO), self-rep. Functioning (SO)	n.a.	Fall incidence (SO)	+ ( $p < 0.01$ )	n.a.	– (n.s.).	0	0	0	0	0	0

(continued)



Weerddesteyn et al. (2006)	IG versus CG (UC) IP = 5 w. OP = 30 w.	$n = 113$ Age: $73 \pm 6-75 \pm 7$ y. COG: ?	IG: Walking/ balance and motor/ cognitive tasks (carrying, memorizing a story)	Standing balance (force platform), ABC (PO)	Walking and cognitive task (obstacle avoidance) (non-val., PO)–Unclear, if assessment included DT	$n$ of falls (PO)	+/- (+ some outcomes, ABC: $p < 0.05$ ; – other: n.s.)	Walking speed not self-selected – If DT assessment	+	(obstacle avoidance $p=0.023$ )	+	$(p < 0.05)$	1	0	0	2
Yamada et al. (2010)	IG versus CG (act) IP = 16 w. OP = 69 w.	$n = 60$ Age: $80 \pm 6$ (IG), $81 \pm 5$ (CG) y. COG: NCI	IG: Walking & cognitive task (TWT/ connecting numbers)	TUG, funct. Reach, one-leg-stand, 10 m walking (SO)	10 m walking and counting, walking and cognitive task (TWT) (part. Val. SO)	$n$ of falls (PO)	+/- (+ TUG $p < 0.01$ ; – other: n.s.)	+	(walking time and steps $p < 0.01$ )	Not given	+	$(p < 0.05)$	1	1	1	4
Yamada et al. (2012)	IG versus CG (act) IP = 24 w. OP = 52 w.	$n = 157$ Age: $86 \pm 6$ (IG), $85 \pm 6$ (CG) y. COG: Mix	IG: Walking and cognitive task (TWT/ connecting numbers)	10-m walking, TUG, funct. Reach, one-leg-stand, obstacle course (SO)	Walking & cognitive task (TWT) (part. Val., SO)	$n$ of falls (PO)	+/- (+ funct. Reach $p = 0.08$ ; – other: n.s.)	+	(performance time $p = 0.02$ )	+	(obstacle contact $p = 0.02$ )	+	$(p < 0.05)$	1	1	4
Yamada et al. (2013)	IG versus CG (act) IP = 24 w. OP = 52 w.	$n = 264$ Age: $76 \pm 9$ (IG), $77 \pm 8$ (CG) y. COG: Mix	IG: Walking and cognitive task (stepping on squares while avoiding other distracters)	TUG, funct. Reach, 10 m walking, STS (unsp.)	Walking and cognitive task (non-val., unsp.)	$n$ of falls (PO)	+/- (+10 m walking, TUG: $p < 0.001$ ; – other: n.s.)	+	(performance time $p < 0.001$ )	+	(stepping fails $p < 0.001$ )	+	$(p < 0.05)$	1	1	4

(continued)

Table 20.1 (continued)

Author (year)	Study design	Sample	DT training	Assessment		Study results			DT quality rating			Overall rating <sup>a</sup>	
				Mobility	DT	Falls	Mobility	DT		DT = objective details	DT training details		DT assess ment
								1st task	2nd task				
Zieschang et al. (2013)	IG versus CG (act) IP = 13 w. OP = 52 w.	n = 91 Age: 82 ± 7 (IG), 83 ± 7 (CG) y. COG: CI	IG: Walking and motor/ cognitive task	STS, maximum strength (PO), walking, stair climbing, POMA, TUG (SO)	n.a.	n of falls, fallers (SO)	+/- maximum strength, walking, climbing, POMA: $p < 0.001$ ; - other: n.s.)	n.a.	n.a.	0	0	0	0

Abbreviations: 5STS 5-chair stand test, ABC Activities specific balance scale, act active (control group activity), BBS Berg Balance Scale, CG control group, COVS Clinical Outcomes Variable Scale, DGI dynamic gait index, DT dual-task, educ. education (control group activity), FIM Functional Independence Measure, funct. functional, IG intervention group, IP intervention period, ind. individual intervention period, mod. modified, n number, n.a. not assessed, n.s. not significant, non-val. non-validated test, Not given DT assessment was conducted, but it remains unclear if secondary task was assessed or if no results for the secondary task are reported, OP observation period, PO primary outcome, POMA Performance Oriented Motor Assessment, PPA Physiological Profile Assessment, PPS Performance-based physical function (consisting of fast walking speed, 5STS, TUG, FICSIT-4 balance test), part. Val. partially validated test, SO secondary outcome, SPPB Short Physical performance battery, STS sit-to-stand test, TUG Timed-Up-and-Go Test, TWT Trail Walking Test, based on the Trail Making Test, unsp. unspecified (outcome), val. validated test, w. weeks, y. years, "+" positive effect, "-" no effect

aRating includes points for "dual-tasking described as study objective," "training details on DT sufficiently described," "DT assessment implemented," and "effects on DT described"

bCOG = cognitive status of the study sample, (NCI = not cognitively impaired, CI = cognitively impaired, mixed = cognitively impaired and intact)

**Publication Year** The articles included had all been published between 2004 and 2017, with more articles published in the recent past ( $n = 22$ ; 2011–2017 [48, 49, 51–54, 56–60, 62–64, 66, 71–74, 76, 77, 79]) as compared to the more distant past ( $n = 10$ ; 2004–2010 [50, 55, 61, 65, 67–70, 75, 78]).

**Study Design** Types of study deviated from each other, with  $n = 23$  studies using an established 2-arm design for 1 intervention group (IG) versus 1 control group (CG) [52–59, 61, 64–72, 75–79].  $N = 6$  studies used a 3-arm design (2 IGs vs. 1 CG; [48–51, 63, 73], with one study using DT training in both IGs [49].  $N = 2$  studies had a 4-arm design (2 IGs vs. 2 CG; [62, 74]; both IGs implemented DT training), and  $n = 1$  study had a 5-arm design (4 IGs vs. 1 CG; [60]), with a nutritional supplementation, cognitive training, physical training (including DT training), combination treatment (including physical/DT training), and usual care control. In  $n = 14$  studies, usual care was used for comparison with the intervention [48, 50, 51, 54, 56, 60, 62, 63, 66, 69, 71, 72, 74, 75], while in  $n = 5$  studies, educational activities represented the CG activity (such as health-related information booklets) [52, 53, 58, 64, 70].  $N = 12$  studies had an active CG, consisting of simple walking (group-based or single training on a treadmill) [49, 59, 65, 76–78], or balance, strength or flexibility exercises [55, 57, 61, 68, 73, 79]. These activities were partially conducted as home-based activities [55, 57, 68, 73]. One study did not describe their CG activity [67].  $N = 27$  studies explicitly focused on exercise interventions with most of these studies combining different exercise components such as strength/resistance, balance, agility training or functional training [48–57, 59, 61, 63–69, 71–73, 76–79].  $N = 5$  studies added other intervention components: Matchar et al. [58] additionally included a screening of vision, polypharmacy, and environmental hazards and Ng et al. [60] compared an exercise program with a nutritional, a cognitive, and a multicomponent program. Swanenburg et al. [70] added a nutritional component (calcium, vitamin D supplementation for all IG and CG subjects). Patil et al. [62] and Uusi-Rasi et al. [74] added a vitamin D supplementation in one of their IGs (exercise) and one of their CGs.

**Study Period** Intervention periods ranged from 2 [71] to 104 [62, 74] weeks (mean: 31 weeks) and total observation periods from 13 [57, 71] to 156 weeks [73] (mean: 53 weeks).

**Sample Size** Sample sizes ranged from  $n = 24$  [70] to 1256 [51] participants with a mean for all studies of  $n = 190$ , altogether including 6086 participants. As studies partly had differed in study design with multiple study groups we also documented mean number of participants per study arm, indicating a wide range from  $n = 12$ –419 (mean:  $n = 77$ ) participants.  $N = 17$  studies had less than 50 participants per study group [48, 49, 54–57, 60, 61, 64, 65, 67–70, 73, 78, 79],  $n = 8$  studies had 50–100 [50, 52, 53, 63, 71, 72, 75, 76], and  $n = 7$  studies had more than 100 [51, 58, 59, 62, 66, 74, 77].

**Age** Mean age of study participants ranged from 67 to 85 (mean age for all studies: 76.8 years.) with  $n = 11$  studies including participants with a mean age  $\geq 80$  years



[48, 50, 55, 57, 64, 67, 71, 73, 76, 78, 79], indicating a high-risk group for falling as defined by age.

**Cognitive Status** Cognitive status of the study sample was defined as not cognitively impaired ( $n = 6$ ; [49, 54, 62, 64, 74, 78]), cognitively impaired ( $n = 2$  [63, 79]), mixed ( $n = 14$  [48, 50, 51, 53, 55, 58–60, 68, 71–73, 76, 77]), or unknown ( $n = 10$  [52, 56, 57, 61, 65–67, 69, 70]). Largest groups were the mixed groups followed by the group with unclear status with both groups not specifying the cognitive status.

**DT Training** In the subgroup of studies which gave details on the DT training ( $n = 20$ ), all studies included a basic/first motor task with walking as the most prominent task ( $n = 11$ ) [50, 51, 54, 58, 65, 68, 69, 73, 76–78];  $n = 1$  walking and stepping [53];  $n = 1$  walking and balance [75];  $n = 3$  balance [55, 60, 61];  $n = 1$  ball games and manual tasks [63];  $n = 1$  walking on a treadmill [59];  $n = 1$  interactive training system [64];  $n = 1$  interactive training system and treadmill [49]. As second tasks, motor and cognitive tasks, such as counting/calculating, clapping every five steps, reading, nominating specific words, carrying objects, looking in different directions, or throwing or catching a ball, were used in  $n = 9$  studies [51, 54, 55, 58, 60, 61, 68, 69, 75]. In  $n = 9$  studies, only cognitive tasks such as memorizing words or objects, counting, or connecting numbers were used as the second task [49, 53, 59, 63–65, 76–78] and in  $n = 2$  studies, the secondary task was only a motor task, for example, turning or carrying objects [50, 73].

The description of the training, especially so when the DT training was only a minor part of the fall prevention program, was often not adequate to clearly understand the training proceedings and the potentially associated impact ( $n = 12$ ; [48, 52, 56, 57, 62, 66, 67, 70–72, 74, 79]). These studies used mostly walking ( $n = 5$  [48, 56, 57, 66, 79]) or balance ( $n = 5$  [52, 62, 70, 71, 74]), in one study ( $n = 1$  [72]), both walking and balance, and in another study ( $n = 1$  [67]) both balance and additional stepping were used as motor tasks. In  $n = 5$  studies, motor and cognitive tasks were combined [48, 52, 66, 67, 79]. In  $n = 2$  studies, only cognitive tasks were included [57, 70], and in  $n = 2$  studies, only motor tasks were included [56, 71].  $N = 3$  studies did not clearly describe whether they used additional motor or cognitive tasks [62, 72, 74].

**Mobility Assessment** Assessment strategies were heterogeneous, mainly covering established clinical mobility tests documenting key motor features such as the Timed-up-and-go, Performance Oriented Mobility Assessment, Berg Balance Scale, Short Physical Performance Battery, or others. Few studies used objective electronical measures such as balance platforms or electronic gait analysis such as the GAITRite system with partly an overlap to DT assessment [49, 54, 55, 59, 67, 70, 72, 73, 75]. Other studies used complex challenging specific tasks related to the training program with a relevant cognitive challenge, partly also used in DT training/assessment such as reaction time tests, 4-square step test, or obstacle avoidance

[52, 65, 76].  $N = 7$  studies used mobility outcomes as a primary end point [48, 52, 54, 60, 63, 73, 75],  $n = 10$  studies had mobility outcomes as a secondary end point [50, 51, 57–59, 66, 69, 74, 76, 78],  $n = 7$  studies used mobility outcomes as both primary and secondary outcomes [49, 53, 55, 70–72, 79], while  $n = 6$  did not specify the priority of the outcomes [56, 61, 62, 65, 67, 77], and  $n = 2$  studies did not assess general mobility [64, 68].

**DT Assessment** These assessments represented the specific method used to evaluate effects of training (specifically the DT training) on DT performances. This variable was also included as a criterion for overall rating to qualify as a DT study (see also scoring for DT quality rating). In  $n = 12$  studies, DT performance was assessed. Among these, DT performance was a primary outcome in  $n = 5$  studies [48, 49, 52, 54, 72], a secondary outcome in  $n = 5$  studies [53, 55, 64, 76, 78], and  $n = 2$  studies did not specify the outcome [61, 77]. Only  $n = 3$  of these studies provided information on the specific outcome parameter for the DT assessment (DT costs [49]; time to complete walking task and obstacle contacts or stepping and avoidance failures [76, 77]).

Eggenberger et al. [49], Trombetti et al. [72], and Yamada et al. 2010 [78] provided information on instructions for the DT assessment (instruction not to prioritize a task [49, 78] or no instruction on prioritizing [72]). All other authors including DT assessment did not provide further information on the assessment procedure or the DT outcomes in the methods. For  $n = 3$  studies, it was unclear whether the assessment included DT, as the description was insufficient (obstacle avoidance [59, 75], stepping in different directions after a signal [65]), thus the studies were poorly rated for the quality scoring item. In  $n = 17$  studies, DT was not assessed [50, 51, 56–58, 60, 62, 63, 66–71, 73, 74, 79].

Among the  $n = 12$  studies that assessed DT,  $n = 3$  studies assessed both tasks (performance duration for the motor task and loss of water [48], respectively obstacle contacts [76] and stepping failure [77]) and  $n = 1$  study assessed the duration for the first task and dual-task costs [49]. For the remaining  $n = 8$  studies, it was unclear whether they assessed the second task or only did not report the results (table comment: not given [52–55, 61, 64, 72, 78]).

**Fall Assessment** Such assessments were included in all 32 studies, as articles had been defined as fall prevention studies, with falls as a major or the primary outcome of the identified trials. Most often, the number of falls (continuous scaling) was used as a relevant study end point ( $n = 27$ ) [49–58, 60, 61, 63–66, 68–70, 72–79], less often the number of fallers (dichotomous scaling) ( $n = 6$ ) [48, 50, 51, 66, 74, 79], the number of injurious falls ( $n = 9$ ) [51, 56–58, 62, 66–68, 74], or other parameters/analyses to document effects of the fall prevention programs such as fall incidence/event rate, or time to first fall ( $n = 6$ ; [50, 55, 59, 62, 67, 71]).

**Effects on Mobility** Most studies included had a focus to improve motor status, representing a high-impact risk factor for falls and a major pathway to effect fall

reduction. However, two studies did not assess mobility outcomes, therefore, no effects had been given [64, 68]. Of the  $n = 30$  studies that assessed mobility outcomes, only  $n = 4$  studies presented exclusively significant improvements for mobility [56, 58, 67, 71], while  $n = 21$  studies had mixed effects [49, 50, 52–54, 59–63, 65, 66, 69, 70, 72, 74–79], and  $n = 5$  studies reported no significant effects for mobility outcomes [48, 51, 55, 57, 73].

**Effects on DT Performance** Among the  $n = 12$  studies with DT assessments,  $n = 7$  reported positive effects for the first (motor) task [49, 53, 54, 64, 76–78],  $n = 1$  study with various DT outcomes reported significant and nonsignificant effects [72], and  $n = 4$  studies reported no effects on the motor task [48, 52, 55, 61]. Out of the three studies that analyzed effects on the secondary tasks,  $n = 2$  studies had significant effects [76, 77], while  $n = 1$  study did not [48].

**Effects on Falls** Among the identified studies,  $n = 15$  (47%) studies reported at least one positive outcome for falls reduction [51, 56, 58, 59, 63, 66–69, 72, 73, 75–78] with an average observation period of 47.5 weeks (range 25–69 weeks) and an average intervention period of 19.3 weeks (range 4–52 weeks), including on average 232 participants per study (range 27–1256). Half of the studies ( $n = 16$ ) reported no significant effect on fall-related outcomes [48–50, 52–55, 57, 60–62, 64, 65, 71, 74, 79], including on average 156 participants per study (range 59–409), with an average intervention period of 29.4 weeks (range 2–104 weeks) and an average observation period of 52.6 weeks (range 13–104 weeks). Two larger studies (354 [56] or 1256 [51] participants) reported positive effects on injurious falls. One study (24 participants) used a different statistical analysis and did not give a p-value on fall-related outcomes [70].  $N = 5$  studies gave results for falls but provided only combined results for both/all IGs, although only one IG respectively not all IGs trained DT, with  $n = 2$  studies reporting positive [63, 73] and  $n = 3$  studies reporting negative results [48, 50, 60].

Among the studies with a single-component design (only exercise including different training elements;  $n = 27$ ; 84%),  $n = 14$  (52%) had significant effects on falls [51, 56, 59, 63, 66–69, 72, 73, 75–78], and  $n = 13$  (48%) reported no significant effects on falls [48–50, 52–55, 57, 61, 64, 65, 71, 79].

Out of the  $n = 5$  studies that used a multicomponent program design (exercise-based and nutritional, cognitive or other components), only Matchar et al. [58] had shown positive results for one of the fall outcomes, while other multicomponent studies had not shown significant effects on falls [60, 62, 74] or had reported no p-value [70].

## DT Quality Rating

**Objective/Background**  $N = 12$  (37.5%) studies mentioned DT as part of the study objective or in the introduction [49, 53, 54, 59, 61, 64, 70, 72, 75–78], while  $n = 20$  (62.5%) did not [48, 50–52, 55–58, 60, 62, 63, 65–69, 71, 73, 74, 79], providing information on DT only in the description of the intervention or in associated articles, that were listed as reference for the description of the intervention.  $N = 6$  (19%) studies explicitly included DT in their objectives, with  $n = 4$  of them

indicating DT as a training component in their objectives [54, 64, 76, 78] and  $n = 2$  mentioning DT in their study title and as a study objective/outcome [49, 72]. Another  $n = 6$  studies provided information on DT training as a relevant part of their introduction to give a background/rationale for their intervention and the relevance of DT for falls reduction [53, 59, 61, 70, 75, 77]. Mean scoring for “objective” was 0.38.

*Description of DT Training*  $N = 20$  (62.5%) gave sufficient details on DT as part of the training description to allow an evaluation/understanding of DT aspects [49–51, 53–55, 58–61, 63–65, 68, 69, 73, 75–78], while  $n = 12$  (37.5%) studies did not specify the DT training or provide a sufficient information on the DT training [48, 52, 56, 57, 62, 66, 67, 70–72, 74, 79]. Mean scoring for “DT training description” was 0.63.

*DT Assessment*  $N = 12$  (37.5%) studies included specific DT assessments [48, 49, 52–55, 61, 64, 72, 76–78], while  $n = 17$  (53.1%) studies did not assess DT [50, 51, 56–58, 60, 62, 63, 66–71, 73, 74, 79] and  $n = 3$  (9.4%) presented an unclear assessment with respect to DT [59, 65, 75]. Among 12 studies with a DT assessment,  $n = 3$  (9%) assessed both tasks [48, 76, 77], while for the remaining  $n = 9$  (28%), it was unclear whether these studies assessed the second task or only did not report results [49, 52–55, 61, 64, 72, 78]. Only 1 study documented DT costs and no study reported combined measures for both tasks [49]. Mean scoring for the criterion “DT assessment” was 0.38.

*Effects on DT Performance*  $N = 7$  studies analyzing DT effects reported significant improvement in at least one DT domain (58%) [49, 53, 54, 64, 76–78]. In  $n = 1$  study, significant and nonsignificant effects (on various gait outcomes) were reported [72].  $N = 3$  studies presented results on both tasks of the DT, with two of them reporting significant effects on both tasks [76, 77] and one reporting no effects on both tasks [48]. Only 1 study presented results as DT costs allowing an adjustment for changes based on single-task performance [49]. No study gave a combined measure for both tasks allowing to document potential prioritization. Mean scoring for the criterion “DT-effect” was 0.38.

*Overall Rating*  $N = 8$  studies [49, 53, 54, 61, 64, 76–78] achieved 4 scores;  $n = 2$  [55, 72] achieved 3 scores;  $n = 4$  [48, 52, 59, 75] achieved 2 scores;  $n = 10$  [50, 51, 58, 60, 63, 65, 68–70, 73] achieved 1 score; and  $n = 8$  [56, 57, 62, 66, 67, 71, 74, 79] achieved 0 scores. Mean overall scoring was 1.5.

## **Association of DT Quality Rating on the Effect of Program to Reduce Falls**

Limited by the small number of studies included in each scoring level and the heterogeneous study design, it seems that the DT quality rating was not clearly associated with effects of intervention on falls with an even distribution of positive and

negative results in each level: level 4 (3 positive/5 negative); level 3 (1 positive/1 negative); Level 2 (2 positive/2 negative); level 1 (3 positive/4 negative/3 mixed results) and level 0 (2 positive/4 negative/1 mixed results).

The  $n = 8$  studies with a maximum rating of 4 points included in average 118 participants (range 59–264) with a mean intervention period of 18 weeks (range 10–26 weeks) and a mean observation period of 46 weeks (range 13–78) [49, 53, 54, 61, 64, 76–78]. Among those  $n = 8$  higher quality DT studies,  $n = 3$  studies (38%) achieved a significant fall reduction (number of participants were 60, 157 and 264) [76–78]. Results are comparable to effects of all included studies with positive fall reduction ( $n = 15$ ; 47%). Among those with no effect on falls reduction within the high-quality trials,  $n = 4$  included a relatively small number of participants ( $n < 100$  [49, 54, 61, 64]), indicating a risk for undersampling with respect to fall prevention, and  $n = 3$  described falls as a secondary outcome [49, 54, 64] or did not specify the outcome status [53], indicating that falls had not been the major focus of their study.

Two studies stood out with respect of a comprehensive DT-strategy and an adequate design for fall prevention [76, 77] leading to a significant fall reduction. Both studies clearly focused on DT as the intervention strategy, included persons of higher age (85/86 respectively 79/77), and at least partly cognitively impaired persons (mixed sample with respect to cognitive impairment), implemented a sufficient observation period (1 year), an adequate sample size for a fall prevention study, and included a well-matched control group with a comparable exercise control activity, but without including dual/multiple tasking in the CG.

---

## Conclusion

Results of the systematic review indicated that DT training was only used in a small number of fall prevention trials. In those studies, which integrated DT training in a comprehensive intervention program or explicitly focused on DT training, the quality of DT training, assessment and result presentation were not adequate when compared to high standards of well-published DT studies with no focus on fall prevention, indicating methodological deficits, which had been described in other reviews evaluating effects of DT training [17, 18, 80, 81]. However, a limited number of high-quality studies achieved positive results with respect to fall prevention as well as DT performances, documenting a proof of concept in this new, clinically oriented research field of combined motor-cognitive training to prevent falls in older people.

## General Study Design

We analyzed design issues in this review with respect to impact of established motor training as well as DT training on effectiveness of fall prevention, as the main outcome in the included fall prevention studies, but also with respect to documentation of potential mechanisms of an effective fall prevention training.

Most studies used a conventional 2-arm design with a randomized IG and CG, but a number of studies also included multiple IGs, thus substantially reducing the sample size per arm with effects on data analysis for fall reduction. Consequently, some studies combined effects for different IGs as compared to the CG to achieve significant results for the rare fall events. Most of the studies focused solely on exercise (partly as different forms of exercise) which was previously described as the superior fall prevention strategy with respect to cost-effectiveness [82, 83] and only a minority of studies identified, used complex, multicomponent interventions.

The quality of the CG activity was heterogeneous with almost half of the studies using rather ill-defined usual care, or unspecific control activities such as educational programs and only a minority of papers included a comparable physical activity program, which might represent a requested quality standard to exclude unspecific intervention effects such as the Hawthorn Effect [84–86].

Falls, especially so injurious falls, representing 5–10 percent of the total number of falls [87], as a clinically most relevant and costly adverse event, represent rare outcomes even in high-risk populations which require large sample sizes to allow documentation of successful interventions in fall prevention. Therefore, well-considered design issues may have to be addressed for a successful fall prevention trial. In the present review, some studies evaded such problems and chose intermediate study end points, such as motor or DT performance as the primary outcome, which may indicate that fall prevention may not have been the major study objective, allowing smaller sample sizes to document effects of intermediate study end points.

However, the use of surrogate end points such as improved mobility might not translate into falls prevention and should be interpreted with caution in the context of falls prevention strategies.

Besides effectiveness of training, duration of intervention, and total observation time influence the sample size calculation [87–89]. For these methodological considerations, a large range of individual study solutions could be documented in this review. Most studies seemed not to have optimized their recruitment process or the study design to prevent undersampling and thereby were not able to achieve significant reduction of fall-related outcomes. Benchmarked against established clinical standards such as the British NICE (National Institute for Health and Care Excellence) guidelines, which rate studies with <200 participants as low quality studies for fall prevention [90], quite a number of studies did not accomplish those standards.

A highly effective strategy to reduce/adjust sample size is to select a study population most affected by a high risk of falling. Among criteria for fall risk stratification, age, and cognitive status stand out, representing high-impact risks for falling in older persons [5, 7]. Age is highly associated with multiple impact factors for falls such as motor decline or deterioration of overall health status [91, 92]. However, in the present review, only a minority of studies comprised participants with a higher age (>80 years.), indicating a frail, potentially multimorbid sample with high risk of falling.

Cognitive status, specifically cognitive impairment, also represents a major risk factor for falls with a substantially increased risk for falls and fall-related events [5, 93, 94]. Among cognitive subdomains, especially dual-task performances may represent a highly relevant missing link between CI and risk of falling, which describes

the potential mechanism and rationale to use DT training in fall prevention. On the other hand, the general cognitive status also describes the risk for specific cognitive deficits such as divided attention as a potential target of DT training. Both arguments therefore point to the high relevance of cognitive status for the patient selection. Surprisingly, only a minority of studies assessed cognitive status without further specification, for example, for DT performance or explicitly focused on persons without CI, despite the fact that cognitive impairment goes along with drastically increased incidence of falls representing a leading risk factor and potential mechanism for falls. With respect to increase cost-effectiveness and effectivity of intervention, a strict recruitment focus on a most affected study sample represents a key strategy and should therefore be prioritized [5, 95].

## **Mobility Assessment**

These assessments were included in this review to document all assessments and effects of the fall prevention programs. In most studies, DT was not the only focus of the training, but was implemented in a more comprehensive approach as indicated by the high number of motor tests as used for primary end points among identified articles. Such design considerations seem appropriate as deficits in overall mobility represent high-risk factors for falls in older people, comparable to cognitive deficits, which have so far not been in the focus of fall prevention studies [96]. Training effects for overall motor performance may therefore compete with those of DT training with respect to effects on falls in such comprehensive intervention programs. Assessment strategies were heterogeneous mainly covering established mobility assessments documenting key motor features which were partly also used in the DT training and assessment methods. Based on the mixed training and assessment design, specific effects of dual-task training on the risk of falling could therefore not be analyzed, thus restricting a detailed analysis of most successful intervention modules.

## **Specific DT Approach**

DT studies were assigned to the physical training domain in fall prevention research, with all identified DT studies related to exercise studies/or reviews including exercise studies. The relationship seems obvious as all DT studies used motor tasks as a primary task in DT training, although DT training targets cognitive (e.g., divided attention) rather than mere motor performances. The future will tell whether the increasing impact of cognitive training – and the understanding of cognition-related mechanisms for falls in older people – will create a new domain in fall prevention research. Although in general, only a small number of studies identified for fall prevention used a DT training approach in their intervention program, a trend to a more frequent inclusion of DT training in fall prevention was visible, documented by the doubled number of DT papers in the recent (2011–2017) compared to the previous publication period (2004–2010).



## Quality Rating

A major aim of the review was to identify and rate quality and comprehensiveness of a DT-based training intervention in the field of fall prevention for which we developed a quality scoring system. Identified studies were heterogeneous with a wide range from merely mentioning the DT approach as a side goal of the intervention to a focused and comprehensive DT-intervention. Lack of “DT quality” was documented by the fact that only 1/3 of the studies explicitly included DT in the study title or at least gave relevant information in the introduction or associated references. Also only one-third of the studies included a specific DT assessment and even less studies ( $n = 3$ ) presented a clear assessment for both tasks in their study outcomes, allowing a comprehensive evaluation. The incomprehensive (or unclear) assessment led to a corresponding number of studies with insufficient documentation of both DTs. Only the description of the training stood out as 2/3 of the studies gave at least a short description, which was sufficient enough to understand the training approach.

Even the highest rated (according to the applied quality scoring in this review) studies, representing a quarter of the studies included, would only qualify for a mandatory minimum reporting standard with respect to DT training, assessment, and data analysis [97, 98]. To meet the requested quality standards of recent DT interventions, comprehensive data analytic methods are mandatory such as DT-cost which allows adjustments for single-task performance (exception ref. [49]), or combined measures of both tasks, which allows accounting for potential prioritization of tasks. A high methodological standard may represent a relevant mean to further improve effectiveness of DT studies in the field of fall prevention and allow a more detailed insight in mechanisms of effects.

## DT Training

DT training was mentioned in all included studies, representing an inclusion criterion for the literature search and the comprehensiveness of the training description was used as a criterion for overall quality rating. Applied training programs were heterogeneous with walking as the most prominent motor component of DT training, followed by balance tasks, both representing key motor features mandatory for mobility-related autonomy. The second task was most often a cognitive task or both motor and cognitive tasks; however, some research groups also focused on motor/motor DT training. Almost all training approaches were based on a rather narrow spectrum of DT training tasks with an overlap from training and test tasks.

In recent high-quality trials, complex DT training approaches were developed to allow a wider transfer from trained to untrained tasks [99, 100] and thereby allowing a more generalized effect of training [101] on cognitive sub-performances such as divided attention as a relevant link to the extraordinary risk of falling in persons with cognitive impairment [11, 12]. Such training concepts could not be identified within included articles, which used

unidimensional training programs highly associated with assessment strategies (e.g., walking and counting as a training and test).

An interesting innovative training approach which also meets the definition of DT training is represented by exergame-based training [102, 103] or virtual reality training which often formally would fulfill criteria for DT training and represent highly motivating and innovative training strategies [104, 105]. We will not discuss these fields of training in detail, as those will further be discussed in another chapter of this book.

## **DT Assessments/Effects**

Results of DT training as identified in the present review also mirrored the insufficient general quality of DT training – and assessment strategy as a prerequisite for documentation of effects of most studies [18, 97, 106]. Only about a third of studies presented any DT results and only about half of those achieved significant improvements of any DT variable, while some studies only gave selected information on outcomes. Results and their presentation partly indicated a limited effectiveness of the training and thereby a limitation to identify potential cognitive mechanisms and their relevance for fall prevention. Only a very small percentage of studies ( $n = 9\%$ ) gave results for both dual-task, which is mandatory to evaluate effects on both tasks as the core criteria for divided attention [97], which also allows to document potential prioritization of tasks or selective trainability of both tasks [107, 108]. Such a comprehensive assessment seems especially relevant when DT training was included in a comprehensive fall prevention program in which established motor training overlaps with DT training addressing similar or identical motor outcomes (e.g., walking as a separate motor training goal and walking as part of a DT). By the given study design, an allocation of effects to the different forms of training is hardly feasible; however, mandatory to evaluate specific effects. Result presentation may indicate that DT may not have been in the focus of the intervention in most studies, but thereby also, that there is space for improvement and effectiveness in DT interventions for fall prevention.

## **Falls Reduction as Associated to Quality of DT Trials**

As identified in the present review, about half of the included studies achieved a significant fall reduction, also including studies with a high DT quality and a clear focus on DT training, which can be rated as a proof of concept that DT strategies may be effective in fall reduction even in those studies, which used an exclusive DT training approach. However, in general, the success rate was not obviously correlated to the quality of the DT approach as documented in this review (quality score), indicating that the DT focus may not have played a major role in all studies with other potential effective strategies applied in interventions with no clear focus on DTs.

## Single- Versus Multicomponent Interventions

By focusing on exercise-based studies in the present review (see exclusion criteria for literature search) it was not feasible to compare a sufficient number of single-versus multicomponent interventions, which are recommended as a primary treatment strategy for falls prevention in the UK [90] and in guidelines for fall prevention by leading medical societies or national commissions on Healthcare [109]. In the present review, the few studies which included physical exercise as a component in multicomponent strategies were not superior to mono-component, exercise-only interventions, confirming results of a most recent Cochrane review [28].

## Limitations

For documentation of results, information as given in the identified articles was used according to predefined review criteria. Authors cannot exclude that additional information had been provided in other sources which may have been relevant for the evaluation but were not accessible for this review.

## Final Remarks and Future Directions

DT training, as well as other forms of cognitive training, have only started to become an established part in fall prevention research and clinical and rehabilitation/prevention practice. To increase the effectiveness and quality of research, future programs may on one hand have to respect basic methodological considerations to design successful fall prevention studies such as adequate sampling by including an adequate length of the observation period, an adequate size of the study sample adjusted for the fall-related study end point (e.g., number of falls vs. number of injurious falls), and a focus on persons most affected by the risk of falling.

On the other hand, to specifically include DT training as a visible and clearly developed focus of intervention, an advanced DT assessment methodology to comprehensively assess effects of intervention as the potential pathway to reduce falls by a cognitive approach, an effective intervention strategy allowing also a transfer of trained tasks into habitual activity behavior, and an adequate selection of the study sample focusing on persons with objectively documented DT deficits may be mandatory. It remains unclear, whether a mixed method/intervention approach might be superior to achieve significant and clinically relevant effects on the risk of falling given the complex and multicausal genesis of falls in old age.

**Acknowledgments** We thank Elena Litz and Michaela Günther-Lange for their support in literature search.

## References

1. Beauchet O, et al. Poor gait performance and prediction of dementia: results from a meta-analysis. *J Am Med Dir Assoc*. 2016;17(6):482–90.
2. Kueper JK, et al. Motor function and incident dementia: a systematic review and meta-analysis. *Age Ageing*. 2017;46(5):729–38.
3. Cohen JA, Verghese J, Zwerling JL. Cognition and gait in older people. *Maturitas*. 2016;93:73–7.
4. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc*. 2001;49(5):664–72.
5. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. *Maturitas*. 2013;75(1):51–61.
6. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: implications for risk assessment and prevention. *J Am Geriatr Soc*. 2018;66(2):367–75.
7. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299–308.
8. Amboni M, Barone P, Hausdorff JM. Cognitive contributions to gait and falls: evidence and implications. *Mov Disord*. 2013;28(11):1520–33.
9. Muir-Hunter SW, Wittwer JE. Dual-task testing to predict falls in community-dwelling older adults: a systematic review. *Physiotherapy*. 2016;102(1):29–40.
10. Naslund J. Visuospatial ability in relation to fall risk and dementia. *Arch Neurol*. 2010;67(5):643.. author reply 643-4
11. Ansai JH, et al. Gait, dual task and history of falls in elderly with preserved cognition, mild cognitive impairment, and mild Alzheimer's disease. *Braz J Phys Ther*. 2017;21(2):144–51.
12. Goncalves J, et al. Dual-task as a predictor of falls in older people with mild cognitive impairment and mild Alzheimer's disease: a prospective cohort study. *Braz J Phys Ther*. 2018;22(5):417–23.
13. Lundin-Olsson L, Nyberg L, Gustafson Y. "Stops walking when talking" as a predictor of falls in elderly people. *Lancet*. 1997;349(9052):617.
14. Hauer K, Marburger C, Oster P. Motor performance deteriorates with simultaneously performed cognitive tasks in geriatric patients. *Arch Phys Med Rehabil*. 2002;83(2):217–23.
15. Hauer K, et al. Cognitive impairment decreases postural control during dual tasks in geriatric patients with a history of severe falls. *J Am Geriatr Soc*. 2003;51(11):1638–44.
16. Rapp K, et al. Epidemiology of falls in residential aged care: analysis of more than 70,000 falls from residents of bavarian nursing homes. *J Am Med Dir Assoc*. 2012;13(2):187.e1–6.
17. Agmon M, et al. A systematic review of interventions conducted in clinical or community settings to improve dual-task postural control in older adults. *Clin Interv Aging*. 2014;9:477–92.
18. Plummer P, et al. Effects of physical exercise interventions on gait-related dual-task interference in older adults: a systematic review and meta-analysis. *Gerontology*. 2015;62(1):94–117.
19. Wollesen B, et al. Feasibility study of dual-task-managing training to improve gait performance of older adults. *Aging Clin Exp Res*. 2015;27(4):447–55.
20. Pichierri G, et al. Cognitive and cognitive-motor interventions affecting physical functioning: a systematic review. *BMC Geriatr*. 2011;11:29.
21. Yogev-Seligmann G, Hausdorff JM, Giladi N. The role of executive function and attention in gait. *Mov Disord*. 2008;23(3):329–42.. quiz 472
22. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture*. 2002;16(1):1–14.
23. Lemke NC, et al. Transferability and sustainability of motor-cognitive dual-task training in patients with dementia: a randomized controlled trial. *Gerontology*. 2018;65(1):68–83.
24. de Bruin ED, van Het Reve E, Murer K. A randomized controlled pilot study assessing the feasibility of combined motor-cognitive training and its effect on gait characteristics in the elderly. *Clin Rehabil*. 2013;27(3):215–25.

25. Schwenk M, et al. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology*. 2010;74(24):1961–8.
26. Cameron ID, et al. Interventions for preventing falls in older people in care facilities and hospitals. *Cochrane Database Syst Rev*. 2012;12:CD005465.
27. Gillespie LD, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2012;9:CD007146.
28. Hopewell S, et al. Multifactorial and multiple component interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. 2018;7:CD012221.
29. Tricco AC, et al. Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis. *JAMA*. 2017;318(17):1687–99.
30. Sherrington C, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. *Br J Sports Med*. 2017;51(24):1750–8.
31. Avanecean D, et al. Effectiveness of patient-centered interventions on falls in the acute care setting compared to usual care: a systematic review. *JBIM Database System Rev Implement Rep*. 2017;15(12):3006–48.
32. Booth V, Hood V, Kearney F. Interventions incorporating physical and cognitive elements to reduce falls risk in cognitively impaired older adults: a systematic review. *JBIM Database System Rev Implement Rep*. 2016;14(5):110–35.
33. Cheng P, et al. Comparative effectiveness of published interventions for elderly fall prevention: a systematic review and network meta-analysis. *Int J Environ Res Public Health*. 2018;15(3):498.
34. Choi SD, et al. Exergame technology and interactive interventions for elderly fall prevention: a systematic literature review. *Appl Ergon*. 2017;65:570–81.
35. Del-Pino-Casado R, Obrero-Gaitan E, Lomas-Vega R. The effect of tai chi on reducing the risk of falling: a systematic review and meta-analysis. *Am J Chin Med*. 2016;44(5):895–906.
36. Francis-Coad J, et al. Effectiveness of complex falls prevention interventions in residential aged care settings: a systematic review. *JBIM Database System Rev Implement Rep*. 2018;16(4):973–1002.
37. Guirguis-Blake JM, et al. Interventions to prevent falls in older adults: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;319(16):1705–16.
38. Lach HW, Harrison BE, Phongphanngam S. Falls and fall prevention in older adults with early-stage dementia: an integrative review. *Res Gerontol Nurs*. 2017;10(3):139–48.
39. Lee SH, Kim HS. Exercise interventions for preventing falls among older people in care facilities: a meta-analysis. *Worldviews Evid-Based Nurs*. 2017;14(1):74–80.
40. Lewis M, Peiris CL, Shields N. Long-term home and community-based exercise programs improve function in community-dwelling older people with cognitive impairment: a systematic review. *J Physiother*. 2017;63(1):23–9.
41. Lomas-Vega R, et al. Tai chi for risk of falls. A meta-analysis. *J Am Geriatr Soc*. 2017;65(9):2037–43.
42. Lopez P, et al. Benefits of resistance training in physically frail elderly: a systematic review. *Aging Clin Exp Res*. 2017;30(8):889–99.
43. McCrum C, et al. A systematic review of gait perturbation paradigms for improving reactive stepping responses and falls risk among healthy older adults. *Eur Rev Aging Phys Act*. 2017;14:3.
44. Naseri C, et al. Reducing falls in older adults recently discharged from hospital: a systematic review and meta-analysis. *Age Ageing*. 2018;47:512.
45. Okubo Y, Schoene D, Lord SR. Step training improves reaction time, gait and balance and reduces falls in older people: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(7):586–93.
46. Robalino S, et al. Effectiveness of interventions aimed at improving physical and psychological outcomes of fall-related injuries in people with dementia: a narrative systematic review. *Syst Rev*. 2018;7(1):31.
47. Veronese N, et al. Dance movement therapy and falls prevention. *Maturitas*. 2017;102:1–5.

48. Ansai JH, et al. Effects of two physical exercise protocols on physical performance related to falls in the oldest old: a randomized controlled trial. *Geriatr Gerontol Int*. 2016;16(4):492–9.
49. Eggenberger P, et al. Multicomponent physical exercise with simultaneous cognitive training to enhance dual-task walking of older adults: a secondary analysis of a 6-month randomized controlled trial with 1-year follow-up. *Clin Interv Aging*. 2015;10:1711–32.
50. Faber MJ, et al. Effects of exercise programs on falls and mobility in frail and pre-frail older adults: a multicenter randomized controlled trial. *Arch Phys Med Rehabil*. 2006;87(7):885–96.
51. Gawler S, et al. Reducing falls among older people in general practice: the ProAct65+ exercise intervention trial. *Arch Gerontol Geriatr*. 2016;67:46–54.
52. Gianoudis J, et al. Effects of a targeted multimodal exercise program incorporating high-speed power training on falls and fracture risk factors in older adults: a community-based randomized controlled trial. *J Bone Miner Res*. 2014;29(1):182–91.
53. Gschwind YJ, et al. ICT-based system to predict and prevent falls (iStoppFalls): results from an international multicenter randomized controlled trial. *Eur Rev Aging Phys Act*. 2015;12:10.
54. Halvarsson A, et al. Long-term effects of new progressive group balance training for elderly people with increased risk of falling – a randomized controlled trial. *Clin Rehabil*. 2013;27(5):450–8.
55. Helbostad JL, Sletvold O, Moe-Nilssen R. Effects of home exercises and group training on functional abilities in home-dwelling older persons with mobility and balance problems. A randomized study. *Aging Clin Exp Res*. 2004;16(2):113–21.
56. Kovacs E, et al. Adapted physical activity is beneficial on balance, functional mobility, quality of life and fall risk in community-dwelling older women: a randomized single-blinded controlled trial. *Eur J Phys Rehabil Med*. 2013;49(3):301–10.
57. Lurie JD, et al. Pilot comparative effectiveness study of surface perturbation treadmill training to prevent falls in older adults. *BMC Geriatr*. 2013;13:49.
58. Matchar DB, et al. Randomized controlled trial of screening, risk modification, and physical therapy to prevent falls among the elderly recently discharged from the emergency department to the community: the steps to avoid falls in the elderly study. *Arch Phys Med Rehabil*. 2017;98(6):1086–96.
59. Mirelman A, et al. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet*. 2016;388(10050):1170–82.
60. Ng TP, et al. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. *Am J Med*. 2015;128(11):1225–1236.e1.
61. Nitz JC, Choy NL. The efficacy of a specific balance-strategy training programme for preventing falls among older people: a pilot randomised controlled trial. *Age Ageing*. 2004;33(1):52–8.
62. Patil R, et al. Effects of a multimodal exercise program on physical function, falls, and injuries in older women: a 2-year community-based, randomized controlled trial. *J Am Geriatr Soc*. 2015;63(7):1306–13.
63. Pitkala KH, et al. Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. *JAMA Intern Med*. 2013;173(10):894–901.
64. Schoene D, et al. Interactive cognitive-motor step training improves cognitive risk factors of falling in older adults – a randomized controlled trial. *PLoS One*. 2015;10(12):e0145161.
65. Shigematsu R, et al. Square-stepping exercise and fall risk factors in older adults: a single-blind, randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2008;63(1):76–82.
66. Siegrist M, et al. Fall prevention in a primary care setting. *Dtsch Arztebl Int*. 2016;113(21):365–72.
67. Sihvonen S, et al. Fall incidence in frail older women after individualized visual feedback-based balance training. *Gerontology*. 2004;50(6):411–6.
68. Skelton D, et al. Tailored group exercise (falls management exercise – FaME) reduces falls in community-dwelling older frequent fallers (an RCT). *Age Ageing*. 2005;34(6):636–9.
69. Smulders E, et al. Efficacy of a short multidisciplinary falls prevention program for elderly persons with osteoporosis and a fall history: a randomized controlled trial. *Arch Phys Med Rehabil*. 2010;91(11):1705–11.

70. Swanenburg J, et al. Effects of exercise and nutrition on postural balance and risk of falling in elderly people with decreased bone mineral density: randomized controlled trial pilot study. *Clin Rehabil.* 2007;21(6):523–34.
71. Treacy D, et al. Additional standing balance circuit classes during inpatient rehabilitation improved balance outcomes: an assessor-blinded randomised controlled trial. *Age Ageing.* 2015;44(4):580–6.
72. Trombetti A, et al. Effect of music-based multitask training on gait, balance, and fall risk in elderly people: a randomized controlled trial. *Arch Intern Med.* 2011;171(6):525–33.
73. Tuunainen E, et al. Postural stability and quality of life after guided and self-training among older adults residing in an institutional setting. *Clin Interv Aging.* 2013;8:1237–46.
74. Uusi-Rasi K, et al. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial. *JAMA Intern Med.* 2015;175(5):703–11.
75. Weerdesteyn V, et al. A five-week exercise program can reduce falls and improve obstacle avoidance in the elderly. *Gerontology.* 2006;52(3):131–41.
76. Yamada M, et al. Complex obstacle negotiation exercise can prevent falls in community-dwelling elderly Japanese aged 75 years and older. *Geriatr Gerontol Int.* 2012;12(3):461–7.
77. Yamada M, et al. Multitarget stepping program in combination with a standardized multicomponent exercise program can prevent falls in community-dwelling older adults: a randomized, controlled trial. *J Am Geriatr Soc.* 2013;61(10):1669–75.
78. Yamada M, et al. Trail-walking exercise and fall risk factors in community-dwelling older adults: preliminary results of a randomized controlled trial. *J Am Geriatr Soc.* 2010;58(10):1946–51.
79. Zieschang T, et al. Sustainability of motor training effects in older people with dementia. *J Alzheimers Dis.* 2013;34(1):191–202.
80. Gobbo S, et al. Effects of exercise on dual-task ability and balance in older adults: a systematic review. *Arch Gerontol Geriatr.* 2014;58(2):177–87.
81. Yang L, et al. Psychometric properties of dual-task balance assessments for older adults: a systematic review. *Maturitas.* 2015;80(4):359–69.
82. Campbell AJ, Robertson MC. Rethinking individual and community fall prevention strategies: a meta-regression comparing single and multifactorial interventions. *Age Ageing.* 2007;36(6):656–62.
83. Davis JC, et al. Does a home-based strength and balance programme in people aged > or =80 years provide the best value for money to prevent falls? A systematic review of economic evaluations of falls prevention interventions. *Br J Sports Med.* 2010;44(2):80–9.
84. Lindheimer JB, O'Connor PJ, Dishman RK. Quantifying the placebo effect in psychological outcomes of exercise training: a meta-analysis of randomized trials. *Sports Med.* 2015;45(5):693–711.
85. Lindquist R, et al. Design of control-group conditions in clinical trials of behavioral interventions. *J Nurs Scholarsh.* 2007;39(3):214–21.
86. Hecksteden A, et al. How to construct, conduct and analyze an exercise training study? *Front Physiol.* 2018;9:1007.
87. Schwenk M, et al. Definitions and methods of measuring and reporting on injurious falls in randomised controlled fall prevention trials: a systematic review. *BMC Med Res Methodol.* 2012;12:50.
88. Gardner MM, Robertson MC, Campbell AJ. Exercise in preventing falls and fall related injuries in older people: a review of randomised controlled trials. *Br J Sports Med.* 2000;34(1):7–17.
89. Province MA, et al. The effects of exercise on falls in elderly patients. A preplanned meta-analysis of the FICSIT trials. Frailty and injuries: cooperative studies of intervention techniques. *JAMA.* 1995;273(17):1341–7.
90. Centre for Clinical Practice at N., National Institute for Health and Care Excellence: Clinical Guidelines, in Falls: Assessment and Prevention of Falls in Older People. 2013, National Institute for Health and Care Excellence (UK).
91. Khow KSF, Visvanathan R. Falls in the aging population. *Clin Geriatr Med.* 2017;33(3):357–68.
92. Grundstrom AC, Guse CE, Layde PM. Risk factors for falls and fall-related injuries in adults 85 years of age and older. *Arch Gerontol Geriatr.* 2012;54(3):421–8.



93. Ambrose AF, Cruz L, Paul G. Falls and fractures: a systematic approach to screening and prevention. *Maturitas*. 2015;82(1):85–93.
94. Fernando E, et al. Risk factors associated with falls in older adults with dementia: a systematic review. *Physiother Can*. 2017;69(2):161–70.
95. Todd C, Skelton D. What are the main risk factors for falls among older people and what are the most effective interventions to prevent these falls? 2004: Copenhagen, WHO Regional Office for Europe.
96. Segev-Jacobovski O, et al. The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? *Expert Rev Neurother*. 2011;11(7):1057–75.
97. Plummer P, Eskes G. Measuring treatment effects on dual-task performance: a framework for research and clinical practice. *Front Hum Neurosci*. 2015;9:225.
98. Montero-Odasso M, et al. Consensus on shared measures of mobility and cognition: from the Canadian Consortium on Neurodegeneration in Aging (CCNA). *J Gerontol A Biol Sci Med Sci*. 2018;74(6):897–909.
99. Lussier M, Brouillard P, Bherer L. Limited benefits of heterogeneous dual-task training on transfer effects in older adults. *J Gerontol B Psychol Sci Soc Sci*. 2017;72(5):801–12.
100. Lussier M, Bugaiska A, Bherer L. Specific transfer effects following variable priority dual-task training in older adults. *Restor Neurol Neurosci*. 2017;35(2):237–50.
101. Fraser S, Bherer L. Age-related decline in divided-attention: from theoretical lab research to practical real-life situations. *Wiley Interdiscip Rev Cogn Sci*. 2013;4(6):623–40.
102. Monteiro-Junior RS, et al. Exergames: neuroplastic hypothesis about cognitive improvement and biological effects on physical function of institutionalized older persons. *Neural Regen Res*. 2016;11(2):201–4.
103. Tait JL, et al. Influence of sequential vs. simultaneous dual-task exercise training on cognitive function in older adults. *Front Aging Neurosci*. 2017;9:368.
104. Molina KI, et al. Virtual reality using games for improving physical functioning in older adults: a systematic review. *J Neuroeng Rehabil*. 2014;11:156.
105. van Diest M, et al. Exergaming for balance training of elderly: state of the art and future developments. *J Neuroeng Rehabil*. 2013;10:101.
106. Commandeur D, et al. Difference scores between single-task and dual-task gait measures are better than clinical measures for detection of fall-risk in community-dwelling older adults. *Gait Posture*. 2018;66:155–9.
107. Plummer P, et al. Texting and walking: effect of environmental setting and task prioritization on dual-task interference in healthy young adults. *Gait Posture*. 2015;41(1):46–51.
108. Agmon M, Kodesh E, Kizony R. The effect of different types of walking on dual-task performance and task prioritization among community-dwelling older adults. *ScientificWorldJournal*. 2014;2014:259547.
109. Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc*. 2011;59(1):148–57.



# Noninvasive Brain Stimulation to Reduce Falls in Older Adults

# 21

Brad Manor, On-Yee Lo, Junhong Zhou, Prabhjot Dhami,  
and Faranak Farzan

## Introduction

Older adults most commonly fall when standing and walking. In addition to an array of spinal and supraspinal neuromuscular reflex arcs, the complex control these two tasks—even when they are carried out quietly within relatively simple environments—requires timely activation of numerous cortical brain regions and their connected neural networks [1, 2]. This cortical control of standing and walking is undoubtedly amplified in “real-life” situations, when our activities of daily living require us to stand or walk in busy, ever-changing environments while completing additional tasks such as talking, reading signs, carrying groceries, or making decisions. The specific cortical networks involved in the control of standing and walking, and the dynamic functional activation patterns that must occur within these networks over multiple temporospatial scales in order to avoid falls, remain largely

---

B. Manor (✉) · O.-Y. Lo · J. Zhou

Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife,  
Boston, MA, USA

Harvard Medical School, Boston, MA, USA

e-mail: [BradManor@hsl.harvard.edu](mailto:BradManor@hsl.harvard.edu)

P. Dhami

Centre for Addiction and Mental Health, Toronto, ON, Canada

Institute of Medical Science, Faculty of Medicine, University of Toronto, Medical Sciences  
Building, 1 King's College Circle, Toronto, ON, Canada

F. Farzan

Centre for Addiction and Mental Health, Toronto, ON, Canada

Institute of Medical Science, Faculty of Medicine, University of Toronto, Medical Sciences  
Building, 1 King's College Circle, Toronto, ON, Canada

School of Mechatronic Systems Engineering, Simon Fraser University, Surrey, BC, Canada

Department of Psychiatry, University of Toronto, Toronto, ON, Canada

© Springer Nature Switzerland AG 2020

M. Montero-Odasso, R. Camicioli (eds.), *Falls and Cognition in Older Persons*,  
[https://doi.org/10.1007/978-3-030-24233-6\\_21](https://doi.org/10.1007/978-3-030-24233-6_21)

373

unknown. Still, studies combining neuroimaging technologies with functional assessments have begun to demonstrate that standing and walking are dependent upon the structural and functional integrity of numerous brain regions [3–5]. Recent studies using portable imaging technologies (e.g., electroencephalography, EEG; functional near-infrared spectroscopy, fNIRS) have further demonstrated that in older adults, standing and walking, especially when dual tasking, activate a host of cortical regions, including those associated with both sensorimotor and cognition function [6–8]. These exciting observations—which will undoubtedly improve in parallel with advances in portable imaging technology—suggest that strategies designed to enhance timely and efficient functional activation within appropriate cortical regions and their connected neural networks hold great promise to improve the control of standing and walking, and ultimately reduce falls, within numerous vulnerable older adult populations.

Noninvasive brain stimulation refers to a collection of technologies that enable selective modulation of cortical function. In this chapter, we highlight two such technologies: transcranial electrical stimulation (tES) and transcranial magnetic stimulation (TMS). Each technology has been applied to human research to manipulate cortical physiology with the expressed goal of augmenting those behaviors that are wanted or beneficial, and/or suppressing those behaviors that are unwanted or disadvantageous to the individual. Both tES and TMS have been employed to maximize function and minimize symptoms across a wide range of diseases or conditions. Considerable effort, for example, has been dedicated to using noninvasive brain stimulation to facilitate motor recovery following stroke, minimize chronic pain, or combat depressive symptoms.

No trials to date have directly studied the effects of noninvasive brain stimulation on prospective fall rates in older adults. Researchers have recently produced preliminary yet promising evidence, however, that tES and TMS may enhance the complex control of standing and walking, augment numerous aspects of cognitive function, and alter several other known factors on the causal pathway to falls in several older adult populations. This chapter will thus introduce tES and TMS technologies and highlight their potential to maximize functional outcomes—and ultimately alleviate the risk of falling—as individuals age into senescence.

---

## Transcranial Electrical Stimulation (tES)

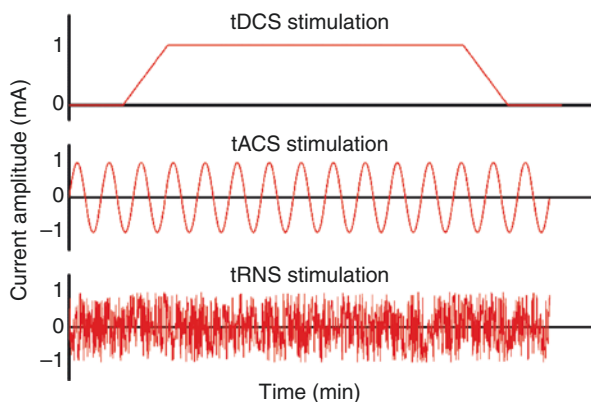
tES is rapidly gaining in popularity within clinical research and is particularly appealing as a therapeutic strategy to reduce falls in older adults: it is low cost and safe when recommended procedures are followed [9], and can be administered using relatively portable equipment. Contrary to some forms of TMS (see section “[Transcranial Magnetic Stimulation \(TMS\)](#)”), tES does not directly induce neuronal activation. It instead modulates cortical excitability (i.e., the likelihood of neuronal firing) by inducing low-amplitude current flow between two or more electrodes placed upon the scalp [10, 11]. A portion of the generated electric field penetrates the scalp and skull, and ultimately, influences brain physiology. The electric field

generated by tES and its online and aftereffects on brain tissue excitability depend upon (1) the type (see following section), intensity, and duration of applied current, (2) the size, polarity, and placement of electrodes [10], and (3) a vast array of anatomical and physiologic properties of the skin, skull, cerebrospinal fluid, and brain tissue.

One particular advantage of implementing tES within clinical studies is that comparative sham stimulation protocols are available. While tES alters the brain's state *directly* via electric fields generated in the cortex, it also *indirectly* affects brain state via the classic placebo effect and by stimulating cutaneous receptors in the skin [12]. Traditional sham protocols deliver stimulation for short period of time (e.g., 30 seconds) before it is “ramped” down to zero for the remainder of the session [13]. This “inactive” sham was adopted because cutaneous sensations associated with tES tend to diminish quickly [14, 15]. Recent evidence, however, suggests that this technique may be suboptimal for double-blinding and “active” sham protocols that vary in current intensity or target are now most typically recommended [16].

## Types of tES

There are several forms of tES that vary in the type of applied current, and thus, their effect on cortical physiology. These forms include transcranial direct current stimulation (tDCS), alternating current stimulation (tACS), and random noise stimulation (tRNS) (Fig. 21.1). While tACS and tRNS offer intriguing opportunities to counteract



**Fig. 21.1** Transcranial electrical stimulation induces subthreshold current flow between electrodes placed upon the scalp. Transcranial direct current stimulation (tDCS) modulates cortical excitability (i.e., the likelihood of neuronal firing) by generating a constant bipolar electric field that polarizes populations of neurons and alters their resting membrane potential. Transcranial alternating current stimulation (tACS) does not induce a polarity offset, but instead generates alternating electric fields with the goal of entraining intrinsic oscillation in brain activity. Transcranial random noise stimulation (tRNS) is believed to amplify weak physiologic signals in the cortex, and thus increase excitability. (Adapted from Tatti et al. [27])

specific age-related changes in brain function, tDCS has been the most widely utilized form of tES to date and will serve as the primary focus of this section.

### **Transcranial Direct Current Stimulation (tDCS)**

tDCS works by inducing constant, low-amplitude current flow between two or more electrodes placed upon the scalp. Current flow is generated by delivering current through at least one “anode” (i.e., positive electrode) and returning it via at least one “cathode” (i.e., negative electrode). This current creates a bipolar electric field within the cortex [11, 17]. tDCS has been traditionally delivered via sponge electrodes with surface areas up to 35 cm<sup>2</sup>. The maximum current delivered through any one electrode is typically limited to 2.0 mA. Most commonly, current is ramped up from zero to maximum output over 30–120 seconds in the beginning of the session, and ramped back down to zero over a similar period of time at the end, in order to ensure patient comfort. Expected side effects using this approach are minimal and most typically include “itching” sensations and skin redness beneath the electrode. Less common side effects include headache and fatigue (for reviews, see Bikson et al. [9] and Antal et al. [18]).

tDCS—especially when delivered via relatively large sponge electrodes—induces a diffuse, bipolar electric field. It has been generally assumed that this electric field facilitates cortical excitability in close proximity to the anode and suppresses cortical excitability in close proximity to the cathode. For example, exposure to 15–30 minutes of tDCS with the anode placed over the primary motor cortex (M1) and the cathode placed on the contralateral supraorbital margin, contralateral M1 area, or contralateral shoulder area has been shown to facilitate cortical excitability, as measured by TMS-induced motor-evoked potentials (MEPs), by up to 40% of baseline levels. Switching the anode and cathode, and thus reversing the direction of current flow, tends to suppress M1 excitability to a similar degree [11, 19]. Importantly, these effects on excitability last for up to 120 minutes following stimulation [20], thereby offering unique opportunities to conduct “cause-and-effect” studies between the brain and behavior. Moreover, repeated exposure to tDCS (e.g., 10 sessions over a 2-week period) has been reported to induce changes in cortical excitability that may be retained for several months [21], thus giving this form of stimulation promise as a therapeutic strategy with long-term benefit.

Recent developments in electric field mapping have proven helpful to our understanding of the effects of tDCS on brain physiology and will undoubtedly shape the future of tDCS (and other forms of tES) research and clinical application. First, modeling studies have indicated that the component of the generated electric field normal to the cortical surface is the key driver of neuronal excitability modulation, likely via its interaction with populations of elongated cortical neurons [10, 22, 23]. Second, modeling work has suggested that interactions between electrode placement and the conductive properties of the head a brain may interact to induce unexpected electric fields at the level of the cortex [24]. This latter concern, in particular, highlights the importance of cathode placement—and important detail with little consistency across published studies.

The generation of unexpected electric fields, together with a lack of personalization of traditional tDCS to individual head and brain anatomy, are likely sources of

often-reported, relatively high intersubject variability in the effects of tDCS intervention on behavioral, functional, and neurophysiologic outcomes [24]. Fortunately, several new technologies have been developed with promise to improve the focality of tDCS, along with the consistency of inducing desired electrical fields within desired brain targets. High-definition tDCS (HD-tDCS) utilizes an array of smaller sponge or gel electrodes in order to more precisely control the flow of electrical current. tDCS optimization algorithms are also now available that enable researchers to determine the electrode placement and current flow parameters that maximize electrical flow to one or more brain regions of interest, while minimizing its effects elsewhere. Such approaches, especially when applied to individual structural and functional MRIs, promise to improve the therapeutic efficacy of this form of noninvasive brain stimulation [25] in the near future.

### **Transcranial Alternating Current Stimulation (tACS)**

tACS is a relatively new form of tES that generates oscillatory electric fields within the brain via the delivery of low-amplitude currents that alternate at a specific frequency (for reviews, see Woods et al. [26] and Tatti et al. [27]). This is accomplished by modulating the direction and amplitude of current flow through each scalp electrode in sinusoidal patterns that are “antiphase” with one another. This form of stimulation is most typically administered without a polarity offset and thus not intended to induce polarity-specific excitation or inhibition of cortical excitability as is tDCS. The goal of tACS is instead to “entrain” specific rhythms within the brain known to be associated with a given cognitive–motor function and/or associated with aging or disease processes. While tACS has been demonstrated to influence brain activity in a frequency specific fashion in younger adults [28–31], its capacity to modulate brain rhythms and benefit functional outcomes in older adults, however, remains largely unexplored.

### **Transcranial Random Noise Stimulation (tRNS)**

tRNS is the newest form of tES. Here, alternating currents are delivered with continuously changing oscillatory frequencies most typically across a wide spectrum (i.e., 0.1–640 Hz) (for review, see Tatti et al. [27]). The effects of tRNS on brain function are still not fully understood; however, observed effects of cortical excitability are theorized to stem from the principle of stochastic resonance [32]. This theory posits that the addition of a certain level of noise (most typically subthreshold) augments the detection and/or transmission of weak physiologic signals [33]. Within the cortex, subthreshold random electric field oscillations thus have the potential to increase cortical excitability without inducing a bipolar electrical field as with tDCS. Similar to tACS, however, the usefulness of tRNS in combating age-related decline in cortical function (in this case excitability) remains to be seen.

## **The Effect of tES on Gait and Postural Control in Older Adults**

Mounting evidence suggests that tES holds promise to improve the control of standing and/or walking in older adults without overt neurological disease. It may also be

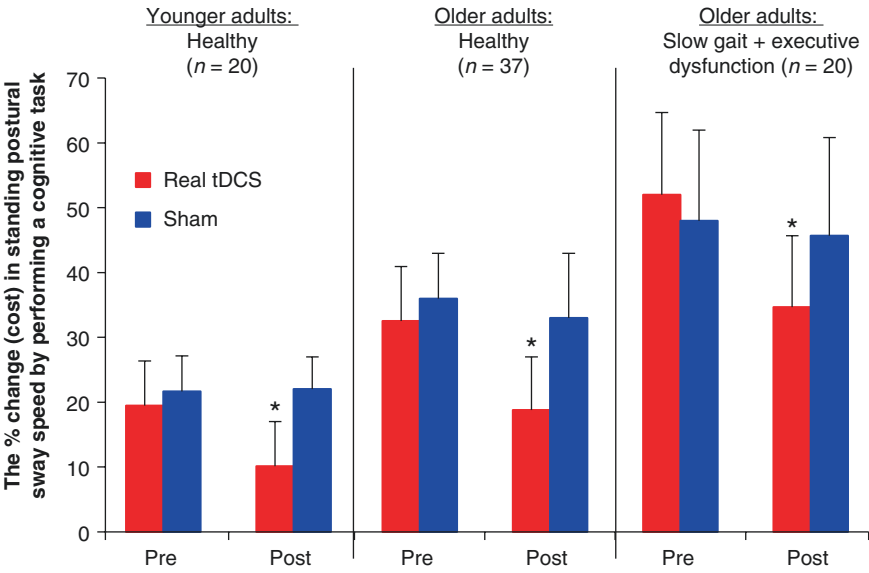
beneficial to those with Parkinson's disease or brain damage following stroke. Most if not all studies to date have utilized tDCS with the intent of facilitating the excitability of either the prefrontal or motor cortices. Available work has examined both the acute effects of a single session of stimulation and/or the longer-term effects of multiple sessions over several consecutive weeks.

Zhou, Manor, and colleagues have published a series of studies suggesting that bipolar tDCS designed to target the left dorsolateral prefrontal cortex (DLPFC) may *acutely* improve the control of standing and walking—especially in “dual-task” situations—in older adults without overt disease or illness. In each of these studies, tDCS was delivered with the participant at rest using 35 cm<sup>2</sup> sponge electrodes at a maximum intensity of 1.5 mA. The anode was placed over the F3 region on the 10–20 EEG electrode placement system and the cathode was placed over the contralateral supraorbital margin. Each participant completed two visits. On one visit, standing and walking were assessed both with and without simultaneous performance of a serial subtraction cognitive task, immediately before and after a single 20-minute session of tDCS. On the other visit, participants completed the same procedures except they received “inactive” sham stimulation. In healthy young adults ( $22 \pm 2$  years) [34], in relatively healthy older adults ( $69 \pm 5$  years) [35], and in older adults ( $81 \pm 10$  years) presenting with both slow gait and mild-to-moderate executive dysfunction [36] neither tDCS nor sham stimulation altered standing postural sway or walking speed under single-task conditions. However, following tDCS, as compared to sham, participants stood with less postural sway speed and area, and walked with faster gait speed, *within dual-task conditions*. As a result, only real tDCS reduced the dual-task cost (i.e., percent change from single to dual tasking) to these variables (Fig. 21.2)—outcomes that have been closely linked to falls risk in older adults [37–39].

Building upon evidence that single sessions of tDCS acutely improved dual-task performance in multiple cohorts, Manor et al. [36] conducted a small sham-controlled, double-blinded, randomized trial to investigate the effects of a multisession tDCS intervention on multiple metrics of cognitive–motor function related to falls risk in older adults [36]. Eighteen older adults without major neurological, musculoskeletal, or cardiorespiratory disease—yet who exhibited both slow gait and mild-to-moderate executive dysfunction—received ten 20-minute sessions of tDCS, or sham stimulation, over a 2-week period. tDCS was designed to target the left DLPFC using characteristics similar to those described in the previous paragraph. Follow-up assessments were completed within 3 days of the final tDCS session and again 2 weeks later. The tDCS intervention group, as compared to sham, exhibited markedly reduced dual-task costs over the 2-week follow-up period (Fig. 21.3). Intriguingly, the tDCS group also exhibited improvements in cognitive function as measured by the Montreal Cognitive Assessment (MoCA), and most specifically, the visuospatial executive function subscore of this test.

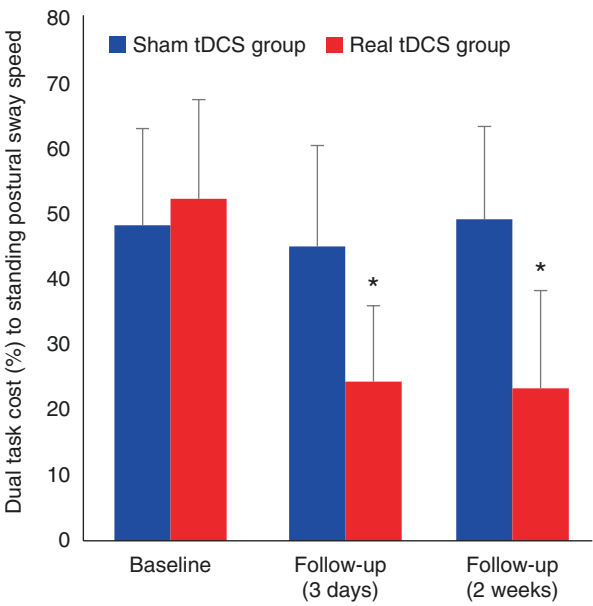
While the above preliminary evidence suggests that tDCS *targeting prefrontal regions* may improve the executive control of gait and balance (i.e., dual tasking), the effects of tDCS targeting the motor cortex or other brain regions or networks





**Fig. 21.2** A single, 20-minute session of tDCS targeting the left dorsolateral prefrontal cortex, as compared to sham, significantly (\*) reduced the dual-task costs to standing balance (i.e., postural sway speed) when testing just following stimulation, in multiple cohorts. Error bars reflect standard error. (Figure created from published data [34–36])

**Fig. 21.3** A 2-week, 10-session intervention of tDCS targeting the left dorsolateral prefrontal cortex, as compared to sham stimulation, significantly (\*) reduced the dual-task cost to standing balance in a small sample of functionally limited older adults without overt disease or illness. Error bars reflect standard error. (Figure created from published data [36])



with known involvement in gait and postural control in aging are still largely unexplored. In one of few other studies, Kaminski et al. [40] examined whether tDCS designed to facilitate the excitability of the primary motor cortex (M1) facilitated learning of a dynamic balance task in 30 healthy older adults. Participants received a single session of tDCS or sham stimulation *while completing balance training task*. The researchers reported that both the group receiving tDCS and the group receiving sham stimulation learned from training, yet that tDCS did not influence the level of task learning. Thus, while tDCS may augment certain aspects of gait and balance in older adults, more research is still needed to determine optimal brain targets and dosage of tDCS, if such interventions should be paired with other evidence-based balance and mobility programs, and ultimately, if improvements in gait and balance indeed translate into reduce risk of falling in older adults who present with increase falls risk, yet without major age-related disease.

Considerably more work has been published on the effects of tDCS in patients with brain damage following stroke and in those with Parkinson's disease (PD). Recent review articles on both stroke [41–43] and PD [44, 45] have similarly concluded that although available evidence lacks consistency in procedures and reporting, and that more definitive trials are still required before translation of tES into clinical practice as a rehabilitative tool, it appears to have a positive impact on the control of standing and/or walking in these patient populations.

A review of tDCS in stroke rehabilitation published in 2017 [43] concluded that noninvasive brain stimulation “can be used to modulate excitability of lower limb muscle (cortical) representations and can lead to improvements in motor performance in stroke survivors.” It also appears that this therapeutic strategy holds the most promise when used as an adjunct therapy along with other evidence-based forms of rehabilitation training [41]. Available intervention studies have typically utilized tDCS to facilitate M1 excitability within the affected hemisphere and/or suppress M1 excitability within the unaffected hemisphere. In a recent study that directly assessed self-reported falls efficacy, Andrade and colleagues [46] examined the effects of 10 once-daily sessions of tDCS over a 2-week period in 60 ambulatory individuals with acute stroke. Participants were randomized to receive tDCS designed to facilitate the excitability of M1 (bilaterally) or sham stimulation. Baseline, posttreatment, 1- and 3-month follow-up assessments included several clinical tests of physical function and the Falls Efficacy Scale. Those participants receiving tDCS, as compared to sham, demonstrated greater improvements in falls efficacy as well as in multiple tests of mobility and lower-limb function. Excitingly, observed group differences were still present 3 months after intervention.

tDCS also appears to have a positive impact on gait and motor symptoms in patients with PD. Similar to stroke rehabilitation, the current body of evidence does not yet point to a clinical recommendation, again largely because of heterogeneity in tDCS intervention characteristics and outcome measures [47]. Potential interactions between tDCS and parkinsonian medications are also relatively poorly understood [45]. As tDCS using current methodology does not appear to generate significant electric fields within deep brain structures, including the basal ganglia, most intervention studies have been designed to modulate excitability of primary

motor and/or prefrontal brain regions. Several of these studies have also focused on functional outcomes linked to falls risk. For example, Lattari et al. [48] examined the effects of a single session of tDCS designed to increase the excitability of the left DLPFC, as compared to sham, in a double-blinded, within-subject, cross-over study in 17 individuals with PD. The intervention and all study assessments were completed with participants in the “on-medication” state. They reported that tDCS, compared to sham, improved performance in several functional field tests linked to falls risk, including the Berg Balance Scale, the Dynamic Gait Index, and the Timed Up and Go (TUG) test. Hadoush et al. [49] conducted a small-scale, randomized, sham-controlled trial on the longer-term effects of a 10-session tDCS intervention in idiopathic PD, but designed stimulation to facilitate the excitability of the bilateral motor and prefrontal areas, as compared to an inactive sham. Participants receiving active stimulation improved performance in the Berg Balance Scale and reported reduced fear of falling as measured by the Falls Efficacy Scale. Most recently, Dagan et al. [50] reported that a single session of “multitarget” tDCS designed to simultaneously facilitate the excitability of the left DLPFC *and* the leg regions of the bilateral M1—as delivered by an array of six gel electrodes with place and current parameters determined using an optimization procedure called Stimweaver™ on a standard brain—reduced the severity of “freezing of gait,” when tested immediately after stimulation, as compared to targeting M1 alone or sham stimulation.

## The Effect of tES on Cognition in Older Adults

tES has been demonstrated to combat—at least in the short term—the effects of aging on numerous aspects of cognitive function that are important to the control of mobility and avoidance of falls in older adults. Tatti et al. [27] published a comprehensive review paper of noninvasive brain stimulation and its effects on cognitive aging and underlying brain physiology in 2016. At that time, 17 studies had been published on the effects of tES on various cognitive outcomes in older adult cohorts. These studies ranged considerably in sample size (from 8 to 106 participants), baseline cognitive status of enrolled participants, the dosage of tES intervention (i.e., intensity and number of sessions), target brain region, and cognitive domain focus (i.e., language, episodic memory, working memory, decision-making, choice reaction time, etc.). Moreover, three of these studies were designed to determine if tDCS might augment the effects of cognitive remediation training. All but one of these 17 studies reported statistically significant, yet not necessarily clinically significant, improvements in cognition when tested immediately after the intervention. While most studies did not assess retention, a handful observed sustained benefits within follow-up assessments as long as 1 month following intervention.

One elegant study published by Stephens and Berryhill [51] highlights the potential for tDCS to mediate cognitive factors related to falls risk in older adults. In that study, 90 cognitively intact older adults completed a 5-day working memory training program. Participants were randomized to receive one of three forms of tDCS

*during working memory training*: inactive sham or tDCS designed to facilitate the excitability of the right prefrontal cortex at an intensity of either 1.0 or 2.0 mA. As expected, each of the three groups improved performance on the specific working memory tasks upon which they trained. The active tDCS groups, as compared to the sham group, also exhibited trends toward improved “near transfer” of learning as measured by two neuropsychological tests of executive function, including a letter span verbal working memory task and a visual *n*-back task, when tested within several days of the intervention. Excitingly, the group who received 2 mA tDCS during training, as compared to the others, demonstrated significant “far transfer” of learning within their own homes at a 1-month follow-up assessment. Specifically, this group of older adults performed better on tasks that assessed their ability to follow rules when scheduling appointments amid distractions (Weekly Calendar Planning Activity) and their driving knowledge, safety awareness, and route planning ability (the Road Law & Road Craft Test). This result—if supported by future research—suggests that tDCS may enhance the effect of cognitive remediation training on transfer of learning to ecologically valid tasks requiring numerous aspects of executive function that are critical to safe mobility during completion of everyday activities.

tDCS may also be suitable to rehabilitate cognitive function in those older adults with mild cognitive impairment or dementia. In a recent study, the same group referenced in the previous paragraph provided evidence that tDCS-induced improvements in working memory—at least in response to a single exposure of stimulation—may be greater in those with relatively low baseline working memory capacity [52]. Moreover, André et al. [53] examined the effects of a four-session tDCS intervention designed to facilitate the excitability of the left dorsolateral prefrontal cortex in 21 older adults with mild vascular dementia. Those receiving tDCS, as compared to sham, exhibited improved performance on the N-back and Go/No-Go tests of executive function over a 2-week follow-up period.

## **The Effects of tES on Other Factors Associated with Falls in Older Adults**

Depression and chronic pain are two issues that have each been closely linked to falls risk as well as mobility decline and cognition dysfunction in older adults [54, 55]. As both depression and chronic pain stem at least in part from cortical dysfunction, considerable effort has and continues to examine the therapeutic potential of tES as a nonpharmacological intervention in these common age-related ailments.

In 2014, a meta-analysis of trials using tDCS as an acute treatment of major depressive disorder suggested that tDCS targeting one or more prefrontal brain regions was significantly superior to sham stimulation in outcomes related to both response and remission of depressive symptoms [56]. Still, relatively few studies have assessed longer-term retention of benefits, especially within geriatric cohorts. Moreover, it is currently unclear if and to what extent observed antidepressive effects of tDCS might translate into improved cognition (see Martin et al. [57] for

meta-analysis) and reduced falls rates, especially in older adults presenting with multiple morbidities.

Mounting evidence also indicates that tDCS may modulate sensory perception thresholds in healthy adults and even reduce pain levels in patient populations. With regard to the former, Zhou et al. [58] published a relevant pilot study suggesting that tDCS may improve the ability to detect tactile stimuli applied to the foot soles when standing. Specifically, the authors demonstrated that a single, 20-minute session of tDCS with the anode over C3 and the cathode over the contralateral supraorbital margin, as compared to sham, significantly improved the threshold at which healthy young adults were able to perceive vibratory stimuli delivered to the foot soles via instrumented insoles. While these results highlight a unique application of tES, it remains to be seen whether these results hold—and translate into improved gait and postural control—in older adults and especially in those with somatosensory impairments.

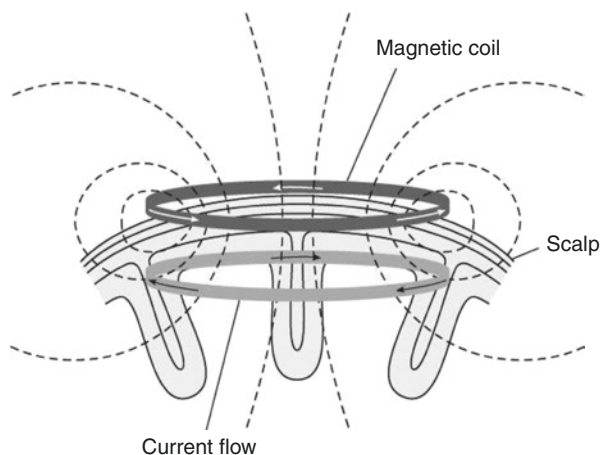
Available trials on chronic pain have focused primarily on fibromyalgia, multiple sclerosis, or migraine, and have typically placed the anode over the C3 or C4 position on the 10–20 EEG electrode placement system (for review, see Pinto et al. [59]). These studies, which again are currently limited by small sample sizes and relatively short follow-ups, generally suggest that tDCS can induce short-term reductions in pain severity as measured by visual analogy pain scales. The capacity for such changes to translate into improved function and reduced falls, again, remains to be seen.

---

## Transcranial Magnetic Stimulation (TMS)

TMS is a noninvasive brain stimulation technique that can modulate the excitability of selected brain regions—and even induce action potentials—via the principle of electromagnetic induction. TMS is administered by placing an induction coil near the scalp over the brain region of interest. Time-varying currents are then passed through the induction coil (Fig. 21.4). Following Faraday’s law of electrical current induction, a time-varying magnetic field is generated perpendicular to the orientation of the coil. This time-varying magnetic field generates a secondary electric current in nearby conductors, including brain structures (e.g., cerebrospinal fluid, gray and white matter) parallel to the coil orientation. Currents induced by TMS can either modulate the state of neuronal excitability (similarly to tES as described in section “[Transcranial Electrical Stimulation \(tES\)](#)”) or cause direct depolarization of neurons and evoke action potentials.

The strength of TMS-induced electrical currents depends upon stimulation parameters, brain tissue properties, and the state of the brain at the time of stimulation. Stimulation parameters include the shape, size, and placement of the TMS coil, as well as the intensity, frequency, and duration of the magnetic pulses. The shape of the coil affects the depth and pattern of the induced electrical field. As such, a variety of coil shapes have been developed to induce different electric fields. The most commonly used coils are figure-of-eight and circular coils, which enable



**Fig. 21.4** Transcranial magnetic stimulation is based on the principle of electromagnetic induction. A magnetic coil is placed above the scalp. The time-varying magnetic field can generate electric current flow parallel to the magnetic coil. This electric field affects the membrane potential of the nearby neurons and other brain structures. Sufficient currents can lead to depolarization of neurons or interference with the ongoing action potentials. (Figure published in Hallett, 2000 *Nature*)

targeting of superficial regions of the cortex (~1.5–3 cm deep). Other coil types, including the double-cone and H-shaped coils, allow electric fields to be generated within relatively deep brain structures (~3–6 cm deep).

Application of a single TMS pulse to the cortex can generate a TMS-evoked potential (TEP) that can be measured with electroencephalography (EEG). TMS applied to the motor cortex in particular can generate a compound action potential resulting in activation of a target muscle within the periphery. This activation can be measured with electromyography (EMG) and is referred to as a motor-evoked potential (MEP). TMS-induced TEPs or MEPs are characterized by their amplitude relative to the intensity of the applied TMS pulse, and/or their latency relative to the applied pulse. Each of these characteristics reflects the integrity of involved cortico-spinal circuitries.

## TMS Protocols

TMS enables assessment of specific aspects of brain functionality—including excitation, inhibition, plasticity, and connectivity—by carefully selecting the intensity, number, and timing of applied pulses through one or more coils that are positioned to influence specific brain regions. To this end, TMS pulses can be delivered one at a time (i.e., single-pulse TMS; one pulse every 5–10 seconds) or in pairs of pulses (i.e., paired-pulse TMS) separated by relatively short (i.e., 1–30 ms) or long (50–200 ms) time intervals. TMS can also be used to modulate cortical excitability by

delivering pulses in repetitive “trains” (i.e., repetitive TMS, or rTMS). rTMS can be delivered at relatively low (i.e., 1–5 Hz) or high (10–20 Hz) frequencies. Theta-burst stimulation (TBS) is another specific type of rTMS in which bursts of 50 Hz rTMS pulses are delivered and repeated within the theta range (5 Hz) as continuous (cTBS) or intermittent trains (iTBS).

### Single-Pulse TMS

The most frequently used single-pulse TMS paradigms include well-established TMS–EMG protocols to probe resting and active motor thresholds, along with the “cortical silent period” in the motor cortex. Single-pulse TMS can also be combined with EEG to study cortical function in nonmotor brain regions. In these protocols, cortical excitation, inhibition, or connectivity are assessed by evaluating the characteristics (e.g., amplitude, latency, or propagation) of TEPs or MEPs induced by a TMS pulse of a specific intensity. When applied to the motor cortex, the intensity and target of the TMS pulse are determined by the EMG outcome measure of interest. For example, the resting motor threshold (RMT) is defined as the minimum stimulation intensity required to generate an MEP with a peak-to-peak amplitude of  $\geq 50 \mu\text{V}$  in 50% of consecutive single pulses, when TMS is applied to the cortical representation, or “hot spot,” of the target muscle [60]. Assessment of active motor threshold (AMT) utilizes a similar TMS procedure, but requires the participant to exert a voluntary contraction of the target muscle while the single TMS pulse is applied (see review by Farzan [61]). To assess the cortical silent period, supra-threshold TMS pulses (e.g., 140% of RMT) are applied to the contralateral motor cortex during voluntary contraction of a target muscle, which results in a period of EMG silence for up to several hundred milliseconds (Fig. 21.5) [62].

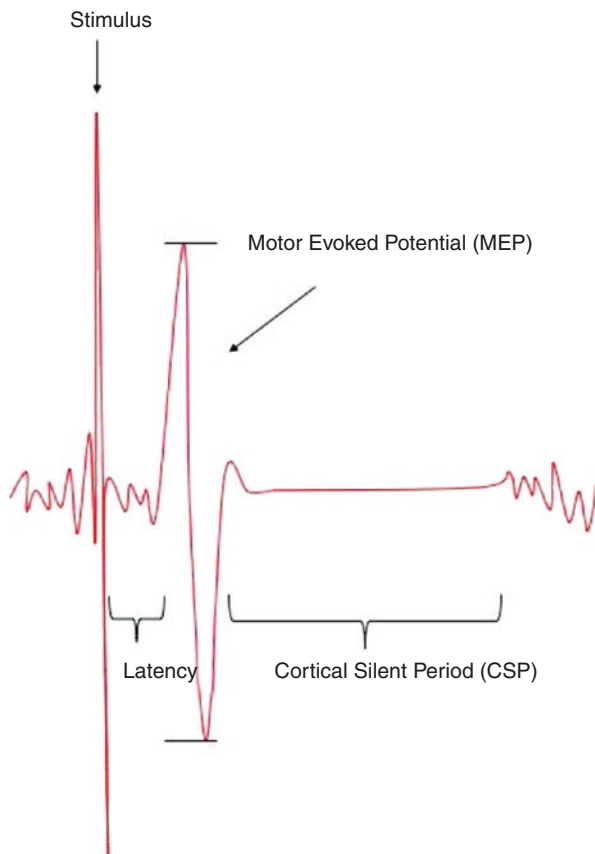
Single-pulse TMS can also be used to assess the functionality of nonmotor brain regions via concurrent EEG recordings (as reviewed in Farzan et al. [63]). Here, the intensity of the TMS pulse is determined using multiple approaches. Some of these approaches include using the threshold determined by EMG outcome measures (e.g., percentage of RMT) in the motor cortex, using EEG outcome measures (e.g., TEP amplitudes), or adjusting the stimulation intensity by estimation of induced electric field (V/m) in the brain areas of interest. While each approach has pros and cons, several characteristics of TEPs, for example, the amplitude of specific negativity or positivity relative to TMS pulse deliver, reflect activation of excitatory or inhibitory processes. Interestingly, early TEP components (e.g., positive or negative peaks with onset latency  $< 30$  ms) are linked to activation of glutamatergic mechanisms, whereas later TEP components (e.g., negativity at 100 ms) are linked with slow-acting GABAergic mechanisms.

### Paired-Pulse TMS

Paired-pulse protocols are used to assess *differences* in MEP or TEP characteristics in response to two TMS pulses, as compared to a single pulse. By manipulating the intensity and interval between paired pulses, the integrity of several meaningful cortical processes can be assessed, including intracortical facilitation (ICF), short interval intracortical inhibition (SICI), long interval intracortical inhibition (LICI),



**Fig. 21.5** Single-pulse TMS. A single TMS pulse (stimulus) of sufficient strength activates cortical neurons that subsequently leads to waves of descending action potentials. Motor-evoked potential (MEP) represents the net effect of multiple neural elements along the pathway. The peak-to-peak amplitude of the MEP indicates the strength or integrity of the corticospinal pathway. MEP latency indicates the time from stimulus delivery to MEP initiation. Following the MEP, TMS effects suppress background EMG activity and lead to a period of inactivity referred to as the cortical silent period (CSP)



interhemispheric inhibition (IHI), cerebellocortical inhibition (CBI), and short-latency afferent inhibition (SAI). For example, to assess LICI, as defined in the motor cortex at rest, two suprathreshold TMS pulses are applied between 50 and 200 ms apart. The induced MEP, as compared to that induced by a single pulse, appears to reflect activation of  $\gamma$ -aminobutyric acid (GABA), and more specifically, GABA<sub>B</sub> receptor-mediated cortical inhibition [64]. Another example is the SICI protocol which involves application of a subthreshold conditioning pulse, rapidly followed by a suprathreshold pulse within 2–6 ms. This protocol, in contrast to LICI, is suggested to probe activation of GABA<sub>A</sub> receptor-mediated cortical inhibition [65].

From a broader perspective, paired-pulse protocols investigate the integrity of a cascade of fast- and slow-acting excitatory and inhibitory processes, occurring either within local cortical circuitry or involving long-range cortico-subcortical feedback loops. Pharmacological studies have also revealed that each protocol appears to reflect the integrity of specific neurotransmitter systems [66].

### **Repetitive TMS (rTMS)**

In general, single- and paired-pulse TMS protocols are not believed to have a significant effect on cortical physiology beyond the stimulation period. In contrast, rTMS, including TBS, is capable of inducing modulation of cortical excitability—either facilitative or suppressive—well beyond the initial stimulation period. Typically, high-frequency rTMS and iTBS leads to excitation of the given cortical region, likely due to a long-term potentiation (LTP)-like effect. In contrast, low-frequency rTMS and cTBS leads to inhibition of excitability within the target region, likely due to its long-term depression (LTD)-like effect. rTMS protocols have thus been applied both to study the functionality of the stimulated brain regions *and* as a therapeutic intervention for multiple neurological and psychological disorders.

### **TMS: A Tool to Probe Cortical Physiology Related to Falls in Aging and Disease**

TMS has been used extensively to study the neurophysiology of aging and age-related disease, along with multiple aspects of motor control linked to gait, balance, and falls in multiple populations. While single- and paired-pulse TMS paradigms are most typically used, rTMS may also be employed to identify causal relationships between the facilitation or inhibition of excitability in *a priori* selected brain regions and cognitive–motor performance.

In general, biological aging has been associated with smaller MEP amplitudes [67] and shorter cortical silent periods [68], more intracortical inhibition and less intracortical facilitation [69], higher resting motor thresholds [70], and potentially, a decrease in LTP-like plasticity [70, 71]. Together, these results suggest that aging reduces cortical excitability and alters the efficiency and malleability of intracortical circuits—neurophysiologic changes that likely diminish sensory integration and cognitive–motor communication within the brain, as well as the capacity to respond to intervention. It is worth noting, however, that the above studies vary considerably in study design and some have in fact reported little or no effect of aging on TMS-derived outcomes, especially with respect to plasticity [72]. Thus, larger prospective studies are warranted to more definitively establish the potential for TMS to provide early biomarkers of aging that underlie functional decline and falls risk in older adults.

TMS has also been used to understand the effects of aging on the complex control of standing and walking. In the first demonstration of TMS, Barker et al. [73] applied TMS to the human motor cortex and used EMG of peripheral musculature to demonstrate the assessment of corticospinal excitability. Development of TMS coils (i.e., the double-cone coil) has since enabled researchers to stimulate deeper cortical regions, including trunk and leg muscle representations in the motor cortex. Numerous studies in younger adults have utilized this technology to demonstrate, for

example, that when walking, MEP amplitudes in lower-limb muscles are dependent upon the current phase of gait cycle [74–77]. TMS to the motor cortex can also alter the intensity of leg muscle activity during walking, both through direct mediation from the cortex to motor neurons and indirect mediation via cortico-cortical neurons in the brain and interneurons in the spine [78–80]. Still other studies have implicated cortical excitability and numerous cortical circuits as important factors in the control of standing postural sway under both quiet and perturbed conditions [81–83].

Together, this elegant line of research highlights the current theory that the control of standing and walking are closely dependent upon numerous “online” control mechanisms involving the cerebral cortex. Strong evidence further indicates that such control is influenced by the aging process, even in the absence of overt disease. For example, Papegaaij et al. [84] used paired-pulse TMS to examine the interaction between age and the excitability of intracortical motor pathways during standing. They reported that older adults exhibited, on average, a ~40% reduction in short-interval intracortical inhibition (SICI) when standing under different conditions (i.e., eyes open or eyes closed, standing on soft or hard surfaces). Such reductions were not observed in younger adults, however, suggesting age-related reorganization of motor cortical circuits involved in locomotor control. Furthermore, studies have also reported that healthy older adults, as compared to young, exhibit relatively greater increases in TMS-derived markers of cortical activity when standing or walking *as task conditions were systematically increased in difficulty*, suggesting that aging heightened reliance upon cortical resources for the regulation of these tasks [85]. Such TMS-derived markers of cortical function—given their sensitivity to aging and demonstrated connection to both gait and postural control—are thus likely the strongest candidates for predicting falls in older adults.

## The Effect of rTMS on Gait and Postural Control in Older Adults

There is an unfortunate lack of studies investigating the potential therapeutic benefits of rTMS for reducing fall risk by improving the control of gait and/or posture in older adults, either with or without cognitive impairment. In contrast, there is a relative wealth of evidence for the use of rTMS for the treatment of motor symptoms in clinical populations. Although not directly translatable to healthy older adults, this evidence suggests that rTMS may be able to enhance gait and/or postural control in numerous age-related diseases. For example, multiple trials have examined the effects of rTMS on mobility-related symptoms of Parkinson’s disease (PD). Khedr et al. [86] reported that an rTMS intervention comprising 2000 daily, 5-Hz supra-threshold pulses over the motor cortex for 10 consecutive days, as compared to a sham intervention, improved performance on the motor portion of the Unified Parkinson’s Disease Rating Scale at a 1-month follow-up visit. The majority of reported trials also suggest that rTMS targeting the motor cortex induces lasting improvement to common metrics related to the control of gait [86–89]. Similarly, rTMS targeting the motor cortex may improve various aspects of gait and posture in various other neurologic diseases or injuries, including stroke [42, 90, 91],

traumatic brain injury [92, 93], multiple sclerosis [94, 95], amyotrophic lateral sclerosis [96, 97], ataxia [98, 99], and dystonia [100, 101]. The retention of observed benefits, as well as their implication for falls risk in these clinical populations, however, remains to be established.

## The Effect of rTMS on Cognition in Older Adults

Although historically limited to motor cortex targeting, advancements in neuroimaging have enabled researchers to utilize TMS to examine and intervene upon the neurophysiology of nonmotor cortical regions, including those subserving cognition. These studies have most commonly assessed the effects of rTMS targeting prefrontal circuits, and particularly neurons within the DLPFC, with hopes of augmenting executive functioning [102, 103]. Such interventions have further attempted to modulate other cognitive and social functions, such as impulse control and emotion regulation. While falls risk outcomes have not been included in these studies, each of the abovementioned aspects of cognition has been linked to falls history and/or prospective falls risk in older adults—making rTMS targeting the prefrontal cortex a promising intervention to augment the executive control of movement and mitigate the risk of falling.

A multitude of studies have investigated the effects of rTMS over the prefrontal cortex on the performance in various cognitive tasks in *healthy young adults*. These studies have collectively demonstrated that rTMS can causally augment numerous cognitive domains, including working memory [104–107], episodic and recognition memory [108], implicit learning [109, 110], response inhibition [111, 112], and response selection [113]. Brunoni and Vanderhasselt [114] in particular reviewed the effects of rTMS over the DLPFC on working memory performance as measured by the *n*-back task. They concluded that healthy adults receiving rTMS over the DLPFC—as compared to sham—were subsequently faster and more accurate in working memory performance, with medium effect sizes for reaction time, correct responses, and error responses. They also noted that the effectiveness of rTMS on *n*-back performance was mediated by numerous cortical factors commonly linked to aging, including neurotransmitter and metabolic pathways [115, 116] and underlying functional and structural connectivity [115, 117, 118].

On the basis of its success in younger adults, there is rapidly growing interest in rTMS as a means of maintaining or enhancing cognition in relatively older adults—particularly with respect to memory. Debarnot et al. [119] reported that excitatory iTBS targeting the left frontopolar cortex, as compared to both inhibitory and sham iTBS, improved prospective memory in a cohort of 30 healthy older adults. Other trials have reported rTMS to improve associative memory [120] and inhibitory control [121]. Interestingly, such rTMS interventions alter cortical activation while healthy older adults are engaged in cognitive tasks, providing evidence that such functional activation can in fact be modulated over time in this population. In one study, Vidal-Pineiro et al. [122] sought to understand the neural changes associated with TMS and its effect on episodic memory. In a pre–post design, healthy older

adults were first scanned using fMRI while engaged in a word encoding memory task. iTBS was then applied over the left inferior frontal gyrus, which was followed by another fMRI while engaged in the same memory task. Changes associated with iTBS included an increase of activity in the left prefrontal and cerebellum–occipital areas during certain types of encoding, as well as in the connectivity between cerebellum–occipital areas and the left inferior frontal region. Sole-Padulles et al. [120] also reported high-frequency rTMS of the prefrontal cortex not only improved associative memory but was also associated with increased activity in the right prefrontal and bilateral posterior cortical regions, as measured by fMRI.

Clinical populations—including mild cognitive impairment, Alzheimer’s disease and related dementia, Parkinson’s disease, and stroke—may also benefit from rTMS targeting prefrontal circuitry. In older adults with mild cognitive impairment, 10 daily sessions of rTMS targeting the DLPFC appears to induce improved memory [123], and potentially, overall cognition [124]. In those with Alzheimer’s disease, such intervention trials have reported enhanced global cognitive functioning [125–128] as well as more specific improvements in memory [125], naming performance [129, 130], auditory comprehension [131], letter and digit cancellation test scores, and inhibitory control [126]. Excitingly, rTMS interventions targeting the DLPFC may also translate into increased capacity to safely perform activities of daily living in older adults with Alzheimer’s disease [125]. Finally, rTMS targeting the DLPFC may improve cognitive–motor function in patients with PD [87, 132] and in those with brain damage following stroke [125, 133, 134]. With respect to stroke, reports indicate that the benefits of rTMS may be sustained for up to 3 months post treatment [125].

## **The Effect of rTMS on Other Factors on the Causal Pathway to Falls**

As highlighted in section “[The Effects of tES on Other Factors Associated with Falls in Older Adults](#)” of this chapter and in numerous previous chapters of this book, depression and chronic pain are two other factors directly linked to falls risk that each stem at least in part from cortical dysfunction. rTMS interventions, in the same light as tES interventions, are thus well positioned to modify each of these risk factors for falls in older adults.

In 2008, the FDA cleared rTMS as a treatment for treatment-resistant depression (FDA approval K061053; K122288). However, it is important to note that the majority of studies to date have focused on patients who are less than 65 years of age. And, results of rTMS trials for depression in older adults, as compared to younger adults, have been less consistent. In a review of brain stimulation treatments for late-life depression, Blumberger et al. [135] concluded that there remains the need for identifying the most appropriate rTMS stimulation parameters for older adults with depression, which may differ from young adults for a multitude of reasons, including cortical atrophy and changes in cortical excitability and functional connectivity [136, 137].

While rTMS appears to be helpful for some types of chronic pain in younger adults, at least over relatively short durations, relatively few studies to date have focused on alleviating pain in older adults. Lefaucheur et al. [138] concluded that while rTMS targeting the motor cortex has been reported to be effective in some studies, considerable research is still needed to determine the types of pain for which noninvasive brain stimulation may be effective. This field will likely advance rapidly as both imaging and TMS studies continue to uncover the cortical networks involved in both the perception and emotional responses to different types of chronic pain—which may then be targeted in hopes of alleviating pain.

---

## Conclusions and Future Directions

A fairly large and rapidly growing body of evidence has built a promising, albeit still preliminary case for both tES and rTMS to serve as safe therapeutic strategies to improve multiple factors on the causal pathway to falls in older adults. These strategies may be particularly suited as adjuncts to other evidence-based interventions including exercise, cognitive remediation, and even medication. Larger, well-controlled, more-definitive trials are thus warranted to help steer the course of this field into the future. Additionally, while large population-based longitudinal studies are lacking, single- and paired-pulse TMS paradigms offer unique opportunities to assess age-related changes in cortical function that may ultimately serve as early biomarkers of fall risk in older adults.

The field of therapeutic noninvasive brain stimulation currently lacks consensus as to the optimal brain regions or networks to target for the promotion of function. In some cases, for example, in stroke rehabilitation, targeting the motor cortices appears poised to facilitate recovery of lower-extremity motor function. In contrast, the most appropriate brain targets to maximize function and ultimately minimize the incidence of falls in older adults remain less clear. It is intriguing to note, however, that interventions targeting prefrontal cognitive networks have shown promise to not only combat the effects of aging and age-related disease on cognition functions linked to fall risk, but also to enhance numerous aspects of gait and postural control, improve mood, and reduce pain in older adults that vary considerably in baseline health and functional status. It is thus reasonable to hypothesize that such prefrontal targets are particularly well suited to induce functional improvements that will hopefully translate into reduced falls in the aged population.

Finally, the majority of published evidence for tES and rTMS interventions in older adults comes from studies that often report moderate-to-high variance in benefits gained across study participants. A large portion of this variance very likely stems from the fact that intervention delivery has most commonly attempted to optimize stimulation based on a “typical” brain and has thus *not* accounted for individual anatomical differences in skin, skull, cerebrospinal fluid, and brain tissue [139]. Both aging and age-related disease amplify these individual differences, influence the conductive properties of each type of involved tissue, may alter

“downstream” effects of stimulation via changes in functional connectivity, and are often accompanied by comorbidities and related medication usage that further influence cortical physiology [140]. Efforts to better understand the complex interactions between noninvasive brain stimulation and each of these interactive confounders are thus desperately needed. In the future, this knowledge is expected to improve the accuracy of current flow modeling and neuronavigation techniques. These technical improvements in turn promise to improve the consistency of tES and rTMS benefits by enabling personalization of interventions to each older adult’s individual brain anatomy and physiology.

## References

1. Fukuyama H, Ouchi Y, Matsuzaki S, et al. Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci Lett*. 1997;228(3):183–6.
2. Miyai I, Tanabe HC, Sase I, et al. Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *NeuroImage*. 2001;14(5):1186–92.
3. Liu J, Hao Y, Du M, et al. Quantitative cerebral blood flow mapping and functional connectivity of postherpetic neuralgia pain: a perfusion fMRI study. *Pain*. 2013;154(1):110–8.
4. Jahn K, Deutschlander A, Stephan T, et al. Imaging human supraspinal locomotor centers in brainstem and cerebellum. *NeuroImage*. 2008;39(2):786–92.
5. Takakusaki K. Neurophysiology of gait: from the spinal cord to the frontal lobe. *Mov Disord*. 2013;28(11):1483–91.
6. Holtzer R, Mahoney JR, Izzetoglu M, Izzetoglu K, Onaral B, Verghese J. fNIRS study of walking and walking while talking in young and old individuals. *J Gerontol A Biol Sci Med Sci*. 2011;66(8):879–87.
7. Doi T, Makizako H, Shimada H, et al. Brain activation during dual-task walking and executive function among older adults with mild cognitive impairment: a fNIRS study. *Aging Clin Exp Res*. 2013;25(5):539–44.
8. Malcolm BR, Foxe JJ, Butler JS, De Sanctis P. The aging brain shows less flexible reallocation of cognitive resources during dual-task walking: a mobile brain/body imaging (MoBI) study. *NeuroImage*. 2015;117:230–42.
9. Bikson M, Grossman P, Thomas C, et al. Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul*. 2016;9(5):641–61.
10. Ruffini G, Wendling F, Merlet I, et al. Transcranial current brain stimulation (tCS): models and technologies. *IEEE Trans Neural Syst Rehabil Eng*. 2013;21(3):333–45.
11. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol*. 2000;527(Pt 3):633–9.
12. Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. *Nat Clin Pract Neurol*. 2007;3(7):383–93.
13. Horvath JC, Carter O, Forte JD. Transcranial direct current stimulation: five important issues we aren’t discussing (but probably should be). *Front Syst Neurosci*. 2014;8:2.
14. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in--short stimulation--fade out approach to sham tDCS--reliable at 1 mA for naïve and experienced subjects, but not investigators. *Brain Stimul*. 2012;5(4):499–504.
15. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul*. 2008;1(3):206–23.
16. Davis NJ, Gold E, Pascual-Leone A, Bracewell RM. Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. *Eur J Neurosci*. 2013;38(7):2973–7.



17. Gandiga PC, Hummel FC, Cohen LG. Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clin Neurophysiol.* 2006;117(4):845–50.
18. Antal A, Alekseichuk I, Bikson M, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol.* 2017;128(9):1774–809.
19. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology.* 2001;57(10):1899–901.
20. Kuo HI, Bikson M, Datta A, et al. Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. *Brain Stimul.* 2013;6(4):644–8.
21. Reis J, Schambra HM, Cohen LG, et al. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proc Natl Acad Sci U S A.* 2009;106(5):1590–5.
22. Ruffini G, Fox MD, Ripolles O, Miranda PC, Pascual-Leone A. Optimization of multifocal transcranial current stimulation for weighted cortical pattern targeting from realistic modeling of electric fields. *NeuroImage.* 2014;89:216–25.
23. Fischer DB, Fried PJ, Ruffini G, et al. Multifocal tDCS targeting the resting state motor network increases cortical excitability beyond traditional tDCS targeting unilateral motor cortex. *NeuroImage.* 2017:157–34.
24. Kim JH, Kim DW, Chang WH, Kim YH, Kim K, Im CH. Inconsistent outcomes of transcranial direct current stimulation may originate from anatomical differences among individuals: electric field simulation using individual MRI data. *Neurosci Lett.* 2014;564:6–10.
25. Datta A, Baker JM, Bikson M, Fridriksson J. Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. *Brain Stimul.* 2011;4(3):169–74.
26. Woods AJ, Antal A, Bikson M, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol.* 2016;127(2):1031–48.
27. Tatti E, Rossi S, Innocenti I, Rossi A, Santarnecchi E. Non-invasive brain stimulation of the aging brain: state of the art and future perspectives. *Ageing Res Rev.* 2016;29:66–89.
28. Ali MM, Sellers KK, Frohlich F. Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *J Neurosci.* 2013;33(27):11262–75.
29. Vossen A, Gross J, Thut G. Alpha power increase after transcranial alternating current stimulation at alpha frequency (alpha-tACS) reflects plastic changes rather than entrainment. *Brain Stimul.* 2015;8(3):499–508.
30. Santarnecchi E, Polizzotto NR, Godone M, et al. Frequency-dependent enhancement of fluid intelligence induced by transcranial oscillatory potentials. *Curr Biol.* 2013;23(15):1449–53.
31. Santarnecchi E, Muller T, Rossi S, et al. Individual differences and specificity of prefrontal gamma frequency-tACS on fluid intelligence capabilities. *Cortex.* 2016;75:33–43.
32. Inukai Y, Saito K, Sasaki R, et al. Comparison of three non-invasive transcranial electrical stimulation methods for increasing cortical excitability. *Front Hum Neurosci.* 2016;10:668.
33. Stacey WC, Durand DM. Stochastic resonance improves signal detection in hippocampal CA1 neurons. *J Neurophysiol.* 2000;83(3):1394–402.
34. Zhou J, Hao Y, Wang Y, et al. Transcranial direct current stimulation reduces the cost of performing a cognitive task on gait and postural control. *Eur J Neurosci.* 2014;39(8):1343–8.
35. Manor B, Zhou J, Jor'dan A, Zhang J, Fang J, Pascual-Leone A. Reduction of dual-task costs by noninvasive modulation of prefrontal activity in healthy elders. *J Cogn Neurosci.* 2016;28(2):275–81.
36. Manor B, Zhou J, Harrison R, et al. tDCS may improve cognitive-motor function in functionally-limited older adults. *Neurorehabil Neural Repair.* 2018; In press
37. Mirelman A, Herman T, Brozgov M, et al. Executive function and falls in older adults: new findings from a five-year prospective study link fall risk to cognition. *PLoS One.* 2012;7(6):e40297.
38. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc.* 2012;60(11):2127–36.

39. Yamada M, Aoyama T, Arai H, et al. Dual-task walk is a reliable predictor of falls in robust elderly adults. *J Am Geriatr Soc.* 2011;59(1):163–4.
40. Kaminski E, Hoff M, Rjosk V, et al. Anodal transcranial direct current stimulation does not facilitate dynamic balance task learning in healthy old adults. *Front Hum Neurosci.* 2017;11:16.
41. Xu Y, Hou QH, Russell SD, et al. Neuroplasticity in post-stroke gait recovery and noninvasive brain stimulation. *Neural Regen Res.* 2015;10(12):2072–80.
42. Chieffo R, Comi G, Leocani L. Noninvasive neuromodulation in poststroke gait disorders: rationale, feasibility, and state of the art. *Neurorehabil Neural Repair.* 2016;30(1):71–82.
43. Fleming MK, Pavlou M, Newham DJ, Sztriha L, Teo JT. Non-invasive brain stimulation for the lower limb after stroke: what do we know so far and what should we be doing next? *Disabil Rehabil.* 2017;39(7):714–20.
44. Brittain JS, Cagnan H. Recent trends in the use of electrical neuromodulation in Parkinson's disease. *Curr Behav Neurosci Rep.* 2018;5(2):170–8.
45. Rektorova I, Anderkova L. Noninvasive brain stimulation and implications for nonmotor symptoms in Parkinson's disease. *Int Rev Neurobiol.* 2017;134:1091–110.
46. Andrade SM, Ferreira JJA, Rufino TS, et al. Effects of different montages of transcranial direct current stimulation on the risk of falls and lower limb function after stroke. *Neurol Res.* 2017;39(12):1037–43.
47. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol.* 2017;128(1):56–92.
48. Lattari E, Costa SS, Campos C, de Oliveira AJ, Machado S, Maranhao Neto GA. Can transcranial direct current stimulation on the dorsolateral prefrontal cortex improves balance and functional mobility in Parkinson's disease? *Neurosci Lett.* 2017;636:165–9.
49. Hadoush H, Al-Jarrah M, Khalil H, Al-Sharman A, Al-Ghazawi S. Bilateral anodal transcranial direct current stimulation effect on balance and fearing of fall in patient with Parkinson's disease. *NeuroRehabilitation.* 2018;42(1):63–8.
50. Dagan M, Herman T, Harrison R, et al. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. *Mov Disord.* 2018;33:642.
51. Stephens JA, Berryhill ME. Older adults improve on everyday tasks after working memory training and neurostimulation. *Brain Stimul.* 2016;9(4):553–9.
52. Arciniega H, Gozenman F, Jones KT, Stephens JA, Berryhill ME. Frontoparietal tDCS benefits visual working memory in older adults with low working memory capacity. *Front Aging Neurosci.* 2018;10:57.
53. Andre S, Heinrich S, Kayser F, et al. At-home tDCS of the left dorsolateral prefrontal cortex improves visual short-term memory in mild vascular dementia. *J Neurol Sci.* 2016;369:185–90.
54. Stubbs B, Stubbs J, Gnanaraj SD, Soundy A. Falls in older adults with major depressive disorder (MDD): a systematic review and exploratory meta-analysis of prospective studies. *Int Psychogeriatr.* 2016;28(1):23–9.
55. Leveille SG, Jones RN, Kiely DK, et al. Chronic musculoskeletal pain and the occurrence of falls in an older population. *JAMA.* 2009;302(20):2214–21.
56. Shiozawa P, Fregni F, Bensenor IM, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *Int J Neuropsychopharmacol.* 2014;17(9):1443–52.
57. Martin DM, Moffa A, Nikolin S, et al. Cognitive effects of transcranial direct current stimulation treatment in patients with major depressive disorder: an individual patient data meta-analysis of randomised, sham-controlled trials. *Neurosci Biobehav Rev.* 2018;90:137–45.
58. Zhou J, Lo OY, Lipsitz LA, Zhang J, Fang J, Manor B. Transcranial direct current stimulation enhances foot sole somatosensation when standing in older adults. *Exp Brain Res.* 2018;236(3):795–802.
59. Pinto CB, Teixeira Costa B, Duarte D, Fregni F. Transcranial direct current stimulation as a therapeutic tool for chronic pain. *J ECT.* 2018;34:e36.
60. Rossini PM, Burke D, Chen R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: basic principles and procedures for rou-

- tine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol.* 2015;126(6):1071–107.
61. Farzan F. Single-pulse transcranial magnetic stimulation (TMS) protocols and outcome measures. In: Rotenberg A, Horvath JC, Pascual-Leone A, editors. *Transcranial magnetic stimulation.* New York: Springer; 2014. p. 69–115.
  62. Inghilleri M, Berardelli A, Cruccu G, Manfredi M. Silent period evoked by transcranial stimulation of the human cortex and cervicomedullary junction. *J Physiol.* 1993;466:521–34.
  63. Farzan F, Vernet M, Shafi MM, Rotenberg A, Daskalakis ZJ, Pascual-Leone A. Characterizing and modulating brain circuitry through transcranial magnetic stimulation combined with electroencephalography. *Front Neural Circuits.* 2016;10:73.
  64. Valls-Sole J, Pascual-Leone A, Wassermann EM, Hallett M. Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalogr Clin Neurophysiol.* 1992;85(6):355–64.
  65. Kujirai T, Caramia MD, Rothwell JC, et al. Corticocortical inhibition in human motor cortex. *J Physiol.* 1993;471:501–19.
  66. Ziemann U. TMS and drugs. *Clin Neurophysiol.* 2004;115(8):1717–29.
  67. Todd G, Kimber TE, Ridding MC, Semmler JG. Reduced motor cortex plasticity following inhibitory rTMS in older adults. *Clin Neurophysiol.* 2010;121(3):441–7.
  68. Oliviero A, Profice P, Tonali PA, et al. Effects of aging on motor cortex excitability. *Neurosci Res.* 2006;55(1):74–7.
  69. McGinley M, Hoffman RL, Russ DW, Thomas JS, Clark BC. Older adults exhibit more intracortical inhibition and less intracortical facilitation than young adults. *Exp Gerontol.* 2010;45(9):671–8.
  70. Bhandari A, Radhu N, Farzan F, et al. A meta-analysis of the effects of aging on motor cortex neurophysiology assessed by transcranial magnetic stimulation. *Clin Neurophysiol.* 2016;127(8):2834–45.
  71. Opie GM, Vosnakis E, Ridding MC, Ziemann U, Semmler JG. Priming theta burst stimulation enhances motor cortex plasticity in young but not old adults. *Brain Stimul.* 2017;10(2):298–304.
  72. Dickins DS, Sale MV, Kamke MR. Plasticity induced by intermittent theta burst stimulation in bilateral motor cortices is not altered in older adults. *Neural Plast.* 2015;2015:323409.
  73. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet.* 1985;1(8437):1106–7.
  74. Schubert M, Curt A, Jensen L, Dietz V. Corticospinal input in human gait: modulation of magnetically evoked motor responses. *Exp Brain Res.* 1997;115(2):234–46.
  75. Ung RV, Imbeault MA, Ethier C, Brizzi L, Capaday C. On the potential role of the corticospinal tract in the control and progressive adaptation of the soleus h-reflex during backward walking. *J Neurophysiol.* 2005;94(2):1133–42.
  76. Petersen TH, Willerslev-Olsen M, Conway BA, Nielsen JB. The motor cortex drives the muscles during walking in human subjects. *J Physiol.* 2012;590(10):2443–52.
  77. Richard A, Van Hamme A, Dreville X, Golmard JL, Meunier S, Welter ML. Contribution of the supplementary motor area and the cerebellum to the anticipatory postural adjustments and execution phases of human gait initiation. *Neuroscience.* 2017;358:181–9.
  78. Petersen N, Christensen LO, Nielsen J. The effect of transcranial magnetic stimulation on the soleus H reflex during human walking. *J Physiol.* 1998;513(Pt 2):599–610.
  79. Petersen NT, Butler JE, Marchand-Pauvert V, et al. Suppression of EMG activity by transcranial magnetic stimulation in human subjects during walking. *J Physiol.* 2001;537(Pt 2):651–6.
  80. Petersen NT, Pyndt HS, Nielsen JB. Investigating human motor control by transcranial magnetic stimulation. *Exp Brain Res.* 2003;152(1):1–16.
  81. Tokuno CD, Taube W, Cresswell AG. An enhanced level of motor cortical excitability during the control of human standing. *Acta Physiol (Oxf).* 2009;195(3):385–95.
  82. Taube W, Schubert M, Gruber M, Beck S, Faist M, Gollhofer A. Direct corticospinal pathways contribute to neuromuscular control of perturbed stance. *J Appl Physiol* (1985). 2006;101(2):420–9.

83. Johannsen L, Hirschauer F, Stadler W, Hermsdorfer J. Disruption of contralateral inferior parietal cortex by 1 Hz repetitive TMS modulates body sway following unpredictable removal of sway-related fingertip feedback. *Neurosci Lett*. 2015;586:13–8.
84. Papegaaij S, Taube W, Hogenhout M, Baudry S, Hortobagyi T. Age-related decrease in motor cortical inhibition during standing under different sensory conditions. *Front Aging Neurosci*. 2014;6:126.
85. Papegaaij S, Taube W, van Keeken HG, Otten E, Baudry S, Hortobagyi T. Postural challenge affects motor cortical activity in young and old adults. *Exp Gerontol*. 2016;73:78–85.
86. Khedr EM, Farweez HM, Islam H. Therapeutic effect of repetitive transcranial magnetic stimulation on motor function in Parkinson's disease patients. *Eur J Neurol*. 2003;10(5):567–72.
87. Dagan M, Herman T, Mirelman A, Giladi N, Hausdorff JM. The role of the prefrontal cortex in freezing of gait in Parkinson's disease: insights from a deep repetitive transcranial magnetic stimulation exploratory study. *Exp Brain Res*. 2017;235(8):2463–72.
88. Kim MS, Chang WH, Cho JW, et al. Efficacy of cumulative high-frequency rTMS on freezing of gait in Parkinson's disease. *Restor Neurol Neurosci*. 2015;33(4):521–30.
89. Lomarev MP, Kanchana S, Bara-Jimenez W, Iyer M, Wassermann EM, Hallett M. Placebo-controlled study of rTMS for the treatment of Parkinson's disease. *Mov Disord*. 2006;21(3):325–31.
90. Dionisio A, Duarte IC, Patricio M, Castelo-Branco M. The use of repetitive transcranial magnetic stimulation for stroke rehabilitation: a systematic review. *J Stroke Cerebrovasc Dis*. 2018;27(1):1–31.
91. Hoyer EH, Celnik PA. Understanding and enhancing motor recovery after stroke using transcranial magnetic stimulation. *Restor Neurol Neurosci*. 2011;29(6):395–409.
92. Dhaliwal SK, Meek BP, Modirrousta MM. Non-invasive brain stimulation for the treatment of symptoms following traumatic brain injury. *Front Psych*. 2015;6:119.
93. Castel-Lacanal E, Tarri M, Loubinoux I, et al. Transcranial magnetic stimulation in brain injury. *Ann Fr Anesth Reanim*. 2014;33(2):83–7.
94. Burhan AM, Subramanian P, Pallaveshi L, Barnes B, Montero-Odasso M. Modulation of the left prefrontal cortex with high frequency repetitive transcranial magnetic stimulation facilitates gait in multiple sclerosis. *Case Rep Neurol Med*. 2015;2015:251829.
95. Iodice R, Manganelli F, Dubbioso R. The therapeutic use of non-invasive brain stimulation in multiple sclerosis—a review. *Restor Neurol Neurosci*. 2017;35(5):497–509.
96. Gibbons C, Pagnini F, Friede T, Young CA. Treatment of fatigue in amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev*. 2018;1:Cd011005.
97. Fang J, Zhou M, Yang M, Zhu C, He L. Repetitive transcranial magnetic stimulation for the treatment of amyotrophic lateral sclerosis or motor neuron disease. *Cochrane Database Syst Rev*. 2013;(5):Cd008554.
98. Farzan F, Wu Y, Manor B, et al. Cerebellar TMS in treatment of a patient with cerebellar ataxia: evidence from clinical, biomechanics and neurophysiological assessments. *Cerebellum*. 2013;12(5):707–12.
99. Kim WS, Jung SH, Oh MK, Min YS, Lim JY, Paik NJ. Effect of repetitive transcranial magnetic stimulation over the cerebellum on patients with ataxia after posterior circulation stroke: a pilot study. *J Rehabil Med*. 2014;46(5):418–23.
100. Lozeron P, Poujois A, Richard A, et al. Contribution of TMS and rTMS in the understanding of the pathophysiology and in the treatment of dystonia. *Front Neural Circuits*. 2016;10:90.
101. Quartarone A, Rizzo V, Terranova C, et al. Therapeutic use of non-invasive brain stimulation in dystonia. *Front Neurosci*. 2017;11:423.
102. Kane MJ, Engle RW. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychon Bull Rev*. 2002;9(4):637–71.
103. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev*. 2006;16(1):17–42.
104. Pascual-Leone A, Hallett M. Induction of errors in a delayed response task by repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. *Neuroreport*. 1994;5(18):2517–20.

105. Mull BR, Seyal M. Transcranial magnetic stimulation of left prefrontal cortex impairs working memory. *Clin Neurophysiol.* 2001;112(9):1672–5.
106. Osaka N, Otsuka Y, Hirose N, et al. Transcranial magnetic stimulation (TMS) applied to left dorsolateral prefrontal cortex disrupts verbal working memory performance in humans. *Neurosci Lett.* 2007;418(3):232–5.
107. Lorenc ES, Lee TG, Chen AJ, D'Esposito M. The effect of disruption of prefrontal cortical function with transcranial magnetic stimulation on visual working memory. *Front Syst Neurosci.* 2015;9:169.
108. Rossi S, Miniussi C, Pascualetti P, Babiloni C, Rossini PM, Cappa SF. Age-related functional changes of prefrontal cortex in long-term memory: a repetitive transcranial magnetic stimulation study. *J Neurosci.* 2004;24(36):7939–44.
109. Pascual-Leone A, Grafman J, Hallett M. Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science.* 1994;263(5151):1287–9.
110. Pascual-Leone A, Wassermann EM, Grafman J, Hallett M. The role of the dorsolateral prefrontal cortex in implicit procedural learning. *Exp Brain Res.* 1996;107(3):479–85.
111. Jahanshahi M, Dirnberger G. The left dorsolateral prefrontal cortex and random generation of responses: studies with transcranial magnetic stimulation. *Neuropsychologia.* 1999;37(2):181–90.
112. Jahanshahi M, Profice P, Brown RG, Ridding MC, Dirnberger G, Rothwell JC. The effects of transcranial magnetic stimulation over the dorsolateral prefrontal cortex on suppression of habitual counting during random number generation. *Brain.* 1998;121(Pt 8):1533–44.
113. Ammon K, Gandevia SC. Transcranial magnetic stimulation can influence the selection of motor programmes. *J Neurol Neurosurg Psychiatry.* 1990;53(8):705–7.
114. Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. *Brain Cogn.* 2014;86:1–9.
115. Noda Y, Zomorodi R, Cash RF, et al. Characterization of the influence of age on GABA<sub>A</sub> and glutamatergic mediated functions in the dorsolateral prefrontal cortex using paired-pulse TMS-EEG. *Aging.* 2017;9(2):556–72.
116. Bridges NR, McKinley RA, Boeke D, et al. Single session low frequency left dorsolateral prefrontal transcranial magnetic stimulation changes neurometabolite relationships in healthy humans. *Front Hum Neurosci.* 2018;12:77.
117. Davis SW, Luber B, Murphy DLK, Lisanby SH, Cabeza R. Frequency-specific neuromodulation of local and distant connectivity in aging and episodic memory function. *Hum Brain Mapp.* 2017;38(12):5987–6004.
118. Schluter RS, Jansen JM, van Holst RJ, van den Brink W, Goudriaan AE. Differential effects of left and right prefrontal high-frequency repetitive transcranial magnetic stimulation on resting-state functional magnetic resonance imaging in healthy individuals. *Brain Connect.* 2018;8(2):60–7.
119. Debarnot U, Crepon B, Orriols E, et al. Intermittent theta burst stimulation over left BA10 enhances virtual reality-based prospective memory in healthy aged subjects. *Neurobiol Aging.* 2015;36(8):2360–9.
120. Sole-Padulles C, Bartres-Faz D, Junque C, et al. Repetitive transcranial magnetic stimulation effects on brain function and cognition among elders with memory dysfunction. A randomized sham-controlled study. *Cereb Cortex.* 2006;16(10):1487–93.
121. Kim SH, Han HJ, Ahn HM, Kim SA, Kim SE. Effects of five daily high-frequency rTMS on Stroop task performance in aging individuals. *Neurosci Res.* 2012;74(3–4):256–60.
122. Vidal-Pineiro D, Martin-Trias P, Arenaza-Urquijo EM, et al. Task-dependent activity and connectivity predict episodic memory network-based responses to brain stimulation in healthy aging. *Brain Stimul.* 2014;7(2):287–96.
123. Koch G, Bonni S, Pellicciari MC, et al. Transcranial magnetic stimulation of the precuneus enhances memory and neural activity in prodromal Alzheimer's disease. *NeuroImage.* 2018;169:302–11.

124. Padala PR, Padala KP, Lensing SY, et al. Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: a double-blind, randomized, sham-controlled, cross-over pilot study. *Psychiatry Res.* 2018;261:312–8.
125. Ahmed MA, Darwish ES, Khedr EM, El Serogy YM, Ali AM. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. *J Neurol.* 2012;259(1):83–92.
126. Antczak J, Kowalska K, Klimkowicz-Mrowiec A, et al. Repetitive transcranial magnetic stimulation for the treatment of cognitive impairment in frontotemporal dementia: an open-label pilot study. *Neuropsychiatr Dis Treat.* 2018;14:749–55.
127. Bentwich J, Dobronevsky E, Aichenbaum S, et al. Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: a proof of concept study. *J Neural Transm (Vienna).* 2011;118(3):463–71.
128. Rabey JM, Dobronevsky E, Aichenbaum S, Gonen O, Marton RG, Khaigrekht M. Repetitive transcranial magnetic stimulation combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: a randomized, double-blind study. *J Neural Transm (Vienna).* 2013;120(5):813–9.
129. Cotelli M, Manenti R, Cappa SF, et al. Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease. *Arch Neurol.* 2006;63(11):1602–4.
130. Cotelli M, Manenti R, Cappa SF, Zanetti O, Miniussi C. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. *Eur J Neurol.* 2008;15(12):1286–92.
131. Cotelli M, Calabria M, Manenti R, et al. Improved language performance in Alzheimer disease following brain stimulation. *J Neurol Neurosurg Psychiatry.* 2011;82(7):794–7.
132. Rektorova I, Sedlackova S, Telecka S, Hlubocky A, Rektor I. Dorsolateral prefrontal cortex: a possible target for modulating dyskinesias in Parkinson's disease by repetitive transcranial magnetic stimulation. *Int J Biomed Imaging.* 2008;2008:372125.
133. Ren CL, Zhang GF, Xia N, et al. Effect of low-frequency rTMS on aphasia in stroke patients: a meta-analysis of randomized controlled trials. *PLoS One.* 2014;9(7):e102557.
134. Lefaucheur JP, Andre-Obadia N, Antal A, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol.* 2014;125(11):2150–206.
135. Blumberger DM, Hsu JH, Daskalakis ZJ. A review of brain stimulation treatments for late-life depression. *Curr Treat Options Psychiatry.* 2015;2(4):413–21.
136. Manes F, Jorge R, Morcuende M, Yamada T, Paradiso S, Robinson RG. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *Int Psychogeriatr.* 2001;13(2):225–31.
137. Mosimann UP, Schmitt W, Greenberg BD, et al. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Res.* 2004;126(2):123–33.
138. Lefaucheur JP, Antal A, Ahdab R, et al. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. *Brain Stimul.* 2008;1(4):337–44.
139. Bikson M, Rahman A, Datta A, Fregni F, Merabet L. High-resolution modeling assisted design of customized and individualized transcranial direct current stimulation protocols. *Neuromodulation.* 2012;15(4):306–15.
140. Seidler RD, Bernard JA, Burutolu TB, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev.* 2010;34(5):721–33.

---

## **Part V**

# **Future Directions and Conclusions**





# Engineering Human Gait and the Potential Role of Wearable Sensors to Monitor Falls

# 22

Ervin Sejdić, Alan Godfrey, William McIlroy,  
and Manuel Montero-Odasso

## Introduction

Falls and falls-related injuries are the major cause of fatal and non-fatal injuries in older adults [1]. It is estimated that close to 640,000 people die from falls globally, and over 37 million falls require medical attention [2]. Falls also lead to fear of falling in older adults, additionally limiting their mobility and productivity, which reduces the overall quality of life and causes further deteriorations in the overall health status [3]. A vicious circle of fear, reduced activity, decreased strength, poor posture, decreased balance and feelings of instability can create a downward spiral resulting in weight loss, illness and depression [2, 4].

---

E. Sejdić (✉)

Department of Electrical and Computer Engineering, Swanson School of Engineering,  
Department of Bioengineering, Swanson School of Engineering, Department of Biomedical  
Informatics, School of Medicine, Intelligent Systems Program, School of Computing and  
Information, University of Pittsburgh, Pittsburgh, PA, USA  
e-mail: [esejdic@ieee.org](mailto:esejdic@ieee.org)

A. Godfrey

Department of Computer and Information Sciences, Northumbria University,  
Newcastle upon Tyne, UK  
e-mail: [alan.godfrey@northumbria.ac.uk](mailto:alan.godfrey@northumbria.ac.uk)

W. McIlroy

Department of Kinesiology, University of Waterloo, Waterloo, ON, Canada  
e-mail: [wmcilroy@uwaterloo.ca](mailto:wmcilroy@uwaterloo.ca)

M. Montero-Odasso

Departments of Medicine (Geriatric Medicine), and Epidemiology and Biostatistics,  
Schulich School of Medicine & Dentistry, University of Western Ontario,  
London, ON, Canada

Gait and Brain Lab, Parkwood Institute, Lawson Health Research Institute,  
London, ON, Canada

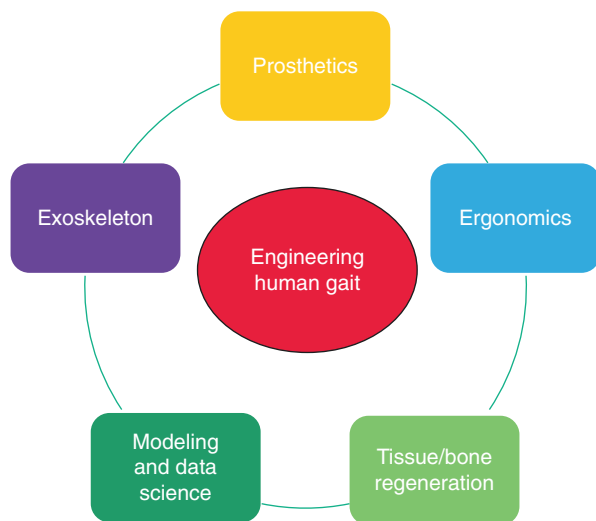
e-mail: [mmontero@uwo.ca](mailto:mmontero@uwo.ca)

Fall risk factors are numerous with details and discussion relating to epidemiology and clinical management extensively covered elsewhere [5–7] in Part I of the current book. In short, the most common fall risk factors include older age, prior history of falls, functional impairment, cognitive impairment or dementia, balance abnormalities and impaired mobility [8]. The ability to discretely and robustly detect and monitor each of these is, therefore, paramount in the safety and care of patients at greatest risk.

Hence, it is obvious that gait represents one of the fundamental human functions needed for independent daily living, and any deteriorations in gait function can have drastic consequences on human health. The fundamentals of gait performance in older adults and their relationship with impairments and falls is reviewed in Chap. 6, Part II, of the current book. Given recent technological advances that enable restoration or advancement of any functions, being human or artificial, this chapter will review approaches to ‘engineer’ gait, which are based on the use of mathematics principles, science, technology and practical knowledge with the goal of restoring or augmenting gait function.

Engineering the human gain function is not a new idea; some of its original developments date back to the ancient Egyptian states [9]. In the last 20–30 years, many different techniques have been proposed and excellent contributions have been made ranging from simple mechanical devices to very complex devices involving multiple sensors and artificial intelligence. While many of these devices and approaches represent early-stage technologies that yet need to see its clinical implementations, Fig. 22.1 describes the current approaches that have direct clinical applications and have already been somewhat clinically implemented: prosthetics, exoskeletons, wearables and modelling of human gait, augmentative devices and engineering and scientific approaches to regenerate tissue/bone.

**Fig. 22.1** Various approaches to engineering human gait



Prosthetics are the oldest and most widely spread engineering solutions that were used for restoring/augmenting human gait [9]. Modern engineering developments in material sciences and other engineering areas have enabled us to develop prosthetics that are lightweight and easily adoptable to different patients, so that end users perform their daily duties with no major altercations [10]. In recent years, we have witnessed a double-leg amputee with prosthetic legs compete in both Paralympics and Olympic Games. While the prosthetic devices used to restore and/or augment human gait have certainly improved in the last 30 years, there are still open questions to be resolved such as their price, which limits their widespread use in developing countries [11, 12].

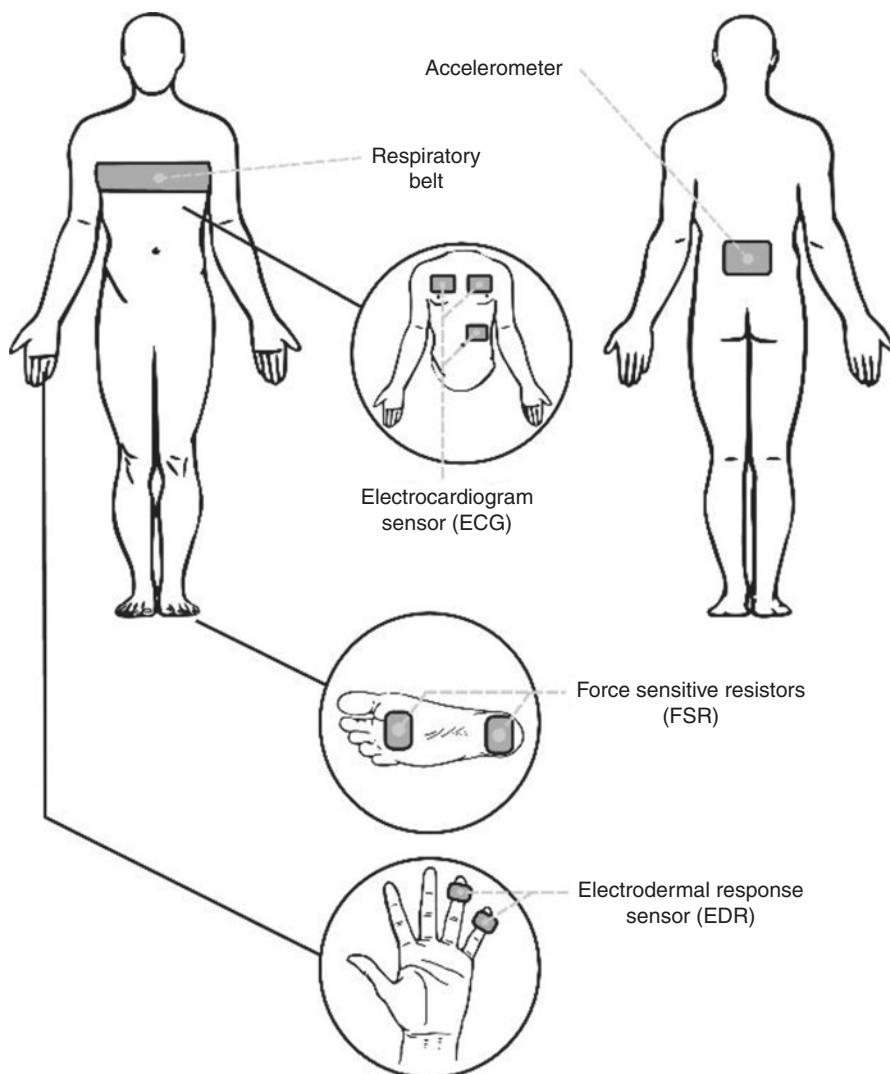
Another traditional line of work is the development of various ergonomic solutions [13, 14]. These range from purely mechanical devices such as a walker that person needs to lift and move with each step to more modern rolling walkers, which enable a person with walking difficulties to move more easily. In more recent years, there are a number of different ideas how to improve these walkers/rollers, but most of them rely on imbedding additional sensors into the walkers [15]. The additional sensors will enable the development of ‘smart’ walkers, which will be able to account for many different real-life cases (e.g. slippery floors) that can endanger the person with walking difficulties [16]. While the technology certainly exists to develop these ‘smart’ walkers/rollers, possible high costs associated with such ‘smart’ devices may prevent their widespread use. Similarly, shoe insoles have been used for many decades to help with walking, and traditional insoles are mechanical devices. In recent years, we have witnessed the development of instrumented insoles that can vibrate at various frequencies in order to stimulate the nerve ends in patients with diminished peripheral nerve sensations or accurately assess gait parameters in real-life settings [17–19]. These instrumented insoles are meant to enhance gait stability and potentially prevent falls in these patient groups. While there is a good clinical evidence that these may actually be very effective in specific clinical groups, there are still no viable commercial products.

More modern developments include exoskeletons, which were initially developed for military applications to augment the soldier’s gait while carrying heavy loads [20]. Soon after the initial development, the exoskeletons have crossed into medical applications, and they are typically used for restoring the gait functions in patients with stroke, spinal cord injuries or similar traumatic injuries [21]. The exoskeletons have not reached their full clinical potential as they remain costly, and there are open questions about their utilization [22, 23]. Namely, about a proper initialization of each step, and if the exoskeletons can be augmented by additional physiological sensors in order to synchronize the step initialization with the rest of the human body [24].

Complex and invasive regenerative medicine methods are emerging to restore/augment the human gait function [25]. These developments typically revolve around bone and/or tissue regeneration to restore the diminished function [26]. Most of the current success stories are focused on repairing a damaged knee cartilage, which will enable patients to walk again without major difficulties. Nevertheless, these tissue/bone regeneration methods are expected to flourish in the future. It is often argued that rehabilitation will play an active role in the

development of regenerative medicine treatments of musculoskeletal disorders, similar to the role it currently plays in the development and the delivery of prosthetic devices or post-operative care.

The most widespread approach to engineer the human gait in recent years relies around the use of wearable sensors, such as accelerometer, inertial measurement units (IMUs) and various other sensors, such as electromyography sensors, respiratory belts, galvanic skin response sensors, to name a few [28]. A sample set of sensors is shown in Fig. 22.2. The use of wearable technology (defined here as



**Fig. 22.2** A set of wearable sensors to assess the interaction between multiple physiological systems during walking [27]

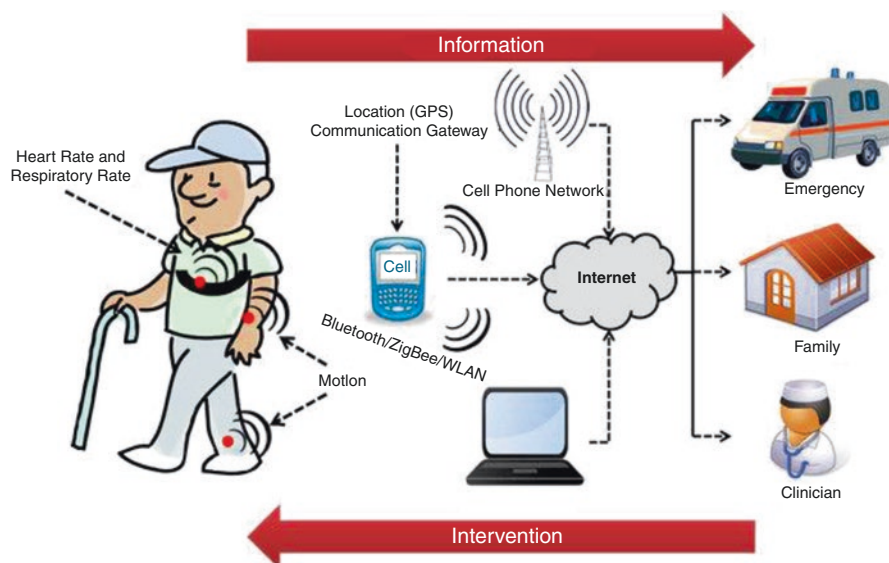
wearables) facilitates the capture of traditional as well as more novel patient-orientated outcomes for fall risk assessment. Indeed, the added benefit of (most) wearables is that the same underlying hardware (i.e. sensors) aids fall detection methodologies. Consequently, wearables offer a holistic tool for the assessment and monitoring of fall-related outcomes. The main reason for the popularity of this approach stems from the fact that these sensors are very affordable, sometimes costing only a dollar or two, are small and can easily interface with commodity electronics such as smartphones and tablets [29]. Using these sensors, different modelling approaches have been adopted over the years to understand gait difficulties or to infer about potential falls. These modelling approaches range from simple one-sensor models such as modelling gait stability using accelerometers or IMUs [30–40] to more complex multi-sensor monitoring to model the interaction among multiple physiological systems during walking [27, 41–43]. The additional benefit of wearable sensors is that they enable us to monitor the gait function even in real-life scenarios such as patients' houses or even when they are walking on a street. This provides an unprecedented opportunity to understand gait beyond typical well-controlled clinical settings and to further understand patients' falls in community settings. It should be mentioned that wearable sensors (i.e. body-worn sensors) can be combined with ambient sensors to assess patients in the home or hospital environment, but in this chapter, we will only focus on wearable sensors.

While each of the aforementioned approaches to engineer the human gait function deserves a thorough coverage, we will focus on wearable sensors in this chapter and their potential to monitor movement (or maybe behaviour) and prevent falls. In the next section, we will introduce a general framework that describes how wearable sensors can be utilized for monitoring gait, and how this field will evolve over the years to improve the clinical outcomes. In the subsequent section, we will cover the most recent contributions dealing with falls monitoring using the wearable sensors. We will briefly review the technological aspects of these contributions, but we will primarily focus on the clinical outcomes.

---

## **Wearable Sensors and Gait**

Remote monitoring of patients during walking is much needed in today's healthcare systems [44]. First, it will enable clinicians to fully understand how the environment affects the gait stability and potential reasons for falls. There is a need to understand how different environmental factors such as lighting, terrain or other auditory and visual distractions affect the gait stability in patients with gait instabilities. Second, remote monitoring also provides a way to monitor patients in rural areas, which often do not have an easy access to clinicians. With a proliferation of consumer electronics and wireless telephony, this until recently unattainable task is becoming reality and is enabling healthcare providers to go beyond 'the walls' of their institutions and provide their services in remote areas. Therefore, wearable sensors and remote monitoring systems have a potential to address these issues, and recent technological and computational advances certainly provide hope for these advancements to address gait instabilities in patients.



**Fig. 22.3** A framework for gait monitoring using wearable sensors [44]

Figure 22.3 illustrates a general framework that can be used for gait monitoring via wearable sensors. This framework would consist of the main components: (1) sensors and other hardware components to collect motion and physiological signals; (2) communication systems to transfer data to and from patients; and (3) data analysis methods to process these data streams and infer about the patient's condition. More specifically, a person with gait difficulties would be typically instrumented with sensors to monitor motion and/or physiological signals during walking. A choice of the sensors would depend on a clinical application, but can include accelerometers (or IMUs), respiratory belts, galvanic skin response sensors, electrocardiograms and others. These sensors can interface with a communication device such as a smartphone, tablet or a computer, which would be connected to the Internet. A cloud-based solution can be then used to analyse streaming data and to infer about the patient's condition and his/her walking. The results of such an analysis can be then conveyed to various entities, such as family members, clinicians or even to alert an emergency service. Lastly, this framework can be potentially used to deliver novel therapies and to monitor the outcomes of such interventions.

There are several open questions about the framework. First and foremost, are there technological barriers? Given the current state of wireless networks, from a data transfer point of view, we are finally at the stage where data transfer does not represent a major issue. Most of the commercial wireless providers have reliable networks with a sufficient bandwidth to support remote monitoring applications in real time. Next, what kind of wearable sensors can we consider? Any sensors that provide details about heart rate, blood pressure, respiratory rate, skin conductance, muscle activity and person's motion are useful, and recent technological

developments have enabled us to obtain accurate, continuous real-time recordings in real-life scenarios. However, it needs to be pointed out that these sensors often require novel design ideas and novel ways to implement them on patients, as many of these existing clinically used sensors to monitor these physiological signals suffer from various artefacts (e.g. due to motion). For example, novel design of sensors can entail that a sensor is a part of a clothing item [45], which also senses the changes in the environment and/or posture and potentially removes any artefacts. Lastly, from a technological point of view, one can ask if sufficient computational algorithms exist to reliably process these data points. Recent advances in machine learning and big data analytics certainly provide sufficient evidence that computational algorithms needed to process these real-time data streams conveying details about the patient's condition have certainly matured into robust algorithms, and researchers and clinicians can rely on them to complete these necessary tasks. Of course, it is understood that most of these algorithms need a certain level of tweaking to accomplish the task, as these algorithms were often developed with other applications in mind.

The second major question is: are there any clinical barriers to adopt the framework for remote monitoring? This is where the idea of remote monitoring becomes more complicated. Some wearable sensors, such as those for heart rate variability, provide traditional clinical measures that clinicians are familiar with and can easily interpret (e.g. heart rate). Sensor developers must often go through rigorous trials to prove that these wearable sensors provide clinically reliable and robust results comparable to the gold-standard equipment found in clinical settings, but once a sensor reliability is established, there are typically no clinical barriers to its implementation. However, sensors such as accelerometers provide novel types of measurements and outcomes [46], which are challenging for clinicians to understand. Many of these novel outcomes represent variables that are not physiological variables (e.g. Lempel–Ziv complexity), and engineers must work directly with clinicians to relate these computational outcomes to actual physiological outcomes and to validate them in clinical trials. Similarly, novel machine-learning approaches often consider hundreds of variables to come up with a reliable decision outcome, and these outcomes may not necessarily have a linear relationship with considered inputs. These nonlinear input–output relationships often pose a problem to clinicians when trying to interpret the outcome in terms of traditional outcomes. Lastly, these machine-learning techniques offer novel ways to consider the interaction between multiple physiological systems to understand how these interactions may influence the gait stability. However, these exciting opportunities provided by novel computational tools are yet fully developed or validated to be implemented in clinical settings. Currently clinical tools are generally limited to a single physiological system without attempting to understand how the interactions with other physiological systems may affect the functional outcome, in this case, gait.

The third major question is: Are there any socio-economical barriers to adopt the framework for remote monitoring? This is a big challenge facing us and not too much research has been completed to answer this question. First, wearables are future medical devices that will need to be prescribed, and the open question is who will issue these prescriptions, a family doctor or a specialist, or even some other healthcare professional such as a physical therapist. Second,



wearable solutions are medical devices whose costs need to be covered. Some insurance entities (public or private) may see them as a great way to reduce costs associated with falls and falls-related injuries, and these entities may be willing to cover the costs of wearables if prescribed by a health professional. However, other insurance entities may not see the benefits and the patient will have to pay for these devices, which can decrease the adoption of a new technology. Third, adopting a new technology among older adults is always challenging, and manufacturers of these wearables will need to carefully address this issue, as patients may not feel comfortable wearing them (e.g. similarly to patients that need a continuous positive airway pressure [CPAP] machine at night). Lastly, many patients may feel that their privacy is violated, as they are equipped with wearables that track almost every move. This is a big concern, as the question is how we regulate sharing of data collected from these wearables. For example, can a GPS location obtained from an IMU be considered a private health data point protected under a legal framework (e.g. the Health Insurance Portability and Accountability Act in the United States)? If not, can these data points be sold by health insurances, sensor manufacturers, healthcare providers or any other entity that has access to these data? As we can see many open social-economic questions are open and will need to be answered before wearables are fully adopted in healthcare systems.

---

## **Wearables**

Wearables come in all shapes and sizes, but preferably, the form factor will be small to facilitate discretion for the wearer during everyday life. Early wearable concepts were bulky and too impractical for seriously consideration as pragmatic devices for monitoring in the home or community. However, the passage of time and advances in microelectromechanical systems ensured the manufacture of hardware components such as inertial sensors, capacitors and resistors became small enough to create wearables to fit neatly on the person. Typically, the user places wearables directly on the skin or by attaching to clothing with clips or other assorted devices. However, wearable placement is of paramount importance when considering the operation of inertial sensors due to their functionality, that is, different sites of attachment will generate different data which impact analysis and sensitivity of detecting required outcomes [47]. The following sections present pragmatic and technical considerations relating to inertial sensor-based wearables, the most common for fall risk and detection. Here, inertial sensors comprise accelerometers and gyroscopes.

### **Inertial Measurement Unit (IMU)**

The terminology surrounding wearables and affiliated technology is diverse. Generally, wearables are the physical unit attached to the wearer and its hardware could comprise any number of sensors and affiliated electrical components (hardware) depending on the measurement need. In the main, memory and battery

configurations dictate wearable form factor, where the latter comprise the majority of weight and space within the wearable. However, future wearables will aim to overcome this pragmatic limitations by utilizing energy harvested from the wearer [28]. IMUs are wearables that primarily utilize accelerometer or gyroscope sensors, which measure acceleration and angular rotation, respectively. These wearables are particularly useful for measuring all aspects of human movement such as duration and intensity. Hence, they have found great utility in measuring aspects of fall risk assessment as encountered earlier: functional impairment, balance abnormalities, and other aspects. Technical reading on inertial sensor functionality can be found elsewhere [48].

IMU development began with sensors attached/strapped to the person with wires/cables running across the body to data loggers attached at the waist. The latter were usually many inches in length, weighted several pounds and worn with a belt attached at that location only. Now, all the functionality exists in a single wearable device no bigger than the end of your thumb. The length of recording depends on the quantity of data recorded (memory) and length of monitoring period (battery life). An IMU for falls (and gait) gather/sample data many times a second (defined as sampling frequency and measured in hertz, Hz) due to the complexity of those activities and the need to define their patterns at high resolutions for more accurate and informed detection. Typically, high sampling rates/frequencies (e.g. 100 Hz) achieve sufficient accuracies. Lower frequencies (e.g. 10 Hz) have utility in movement analysis but generally confined to broader aspects of human movement such as ambulatory activity or energy expenditure.

IMUs with multiple accelerometer and/or gyroscope sensors and high sampling frequencies are more readily suitable for laboratory use, collecting data in predefined patterns with the aid of structured testing protocols during short durations. Although they could be used in home-based environments, it would greatly increase the logistical complexity of deployment, data management and deciphering/interpretation if not adequately supervised through direct observation or accompanied by video recording. To understand data and overcome complexity, that is, understanding what movement is collected, IMUs have been developed for specific purposes/tasks, individual aspects of human movement. Typically, those tasks are informed by traditional *pen and papers* methods, tried and trusted techniques to inform patient diagnosis based on decades worth of research. In short, commercial IMUs generally align to testing specific aspects of traditional physical capability assessment, for example, gait (GaitUp<sup>1</sup>) and timed-up-and-go (TUG, Kinesis<sup>2</sup>) have shown utility in assessing frailty in older adults. The commercial technologies listed help quantify macro (broad) as well as micro (fine) motor characteristics of movement. The latter traditionally attainable in bespoke facilities only (e.g. biomechanics laboratories) with more expensive, fixed location equipment. Of greater utility for future patient, assessment will be the holistic approach to movement quantification with single or small set of IMUs optimized to gather relevant multiple macro and micro outcomes.

---

<sup>1</sup> [www.gaitup.com](http://www.gaitup.com)

<sup>2</sup> [www.kinesis.ie](http://www.kinesis.ie)

This is possible with the fusion of numerous IMU algorithms to gather gait, TUG, balance and postural transitions [49]. The use of such innovative approaches can bring the expertise of an in-depth clinical assessment into the comforts of a patient's own natural surroundings, minimize disruption and ease burden. Nevertheless, the widespread adoption of such technologies remains sparse due to educational upskilling of frontline healthcare professionals and data privacy and control. The latter remains an ever-evolving quandary for this age of technology development with blurred lines between the use of IMUs/wearables as diagnostics and transfer of data between stakeholders and organizations in healthcare [50]. Indeed, wearable education needs to extend beyond frontline clinical staff to the direct beneficiaries of their use, elderly populations more prone to disease and in need of continuous monitoring to ensure good health. A recent study detailed a need to create awareness and knowledge among this group as wearables emerge as aids to detect and prevent medical [51].

## Video

Perhaps, the use and immediate transfer of IMU data is more readily achievable within health services due to the easier implementation of non-identifiable data. Commonly, IMUs with programming software will ask users/researchers to input generic study details, for example, unique patient identification (ID) number, testing session ID, study name.<sup>3</sup> The patient ID will be recorded and referenced to a paper or digital record stored securely in a controlled and safe location accessible by the research team only via a key or password, respectively. Therefore, this aids patient confidentiality as no clearly identifiable information is recorded via the IMU. Alternatively, the use of video recording raises pragmatic questions for IMU development that remain unanswered. To date, IMUs are validated in controlled environments under direct observation, researchers manually observing or video recording activities. The latter are assessed against the direct output classification of IMU data with associated algorithms. One simple example includes number of steps manually counted vs. number of steps quantified by the IMU system (hardware, data and software/algorithms). Another example involves the use of a volunteer performing numerous activities of daily living (ADL, e.g., walking upstairs, getting dressed) and performing a simulated fall onto crash mats. The second example usually involves a researcher video recording all activities and noting when the volunteer performed a fall. The type of fall<sup>4</sup> as well as the exact time will be checked against (i) the accuracy of the IMU data (does the data visually infer a fall event)

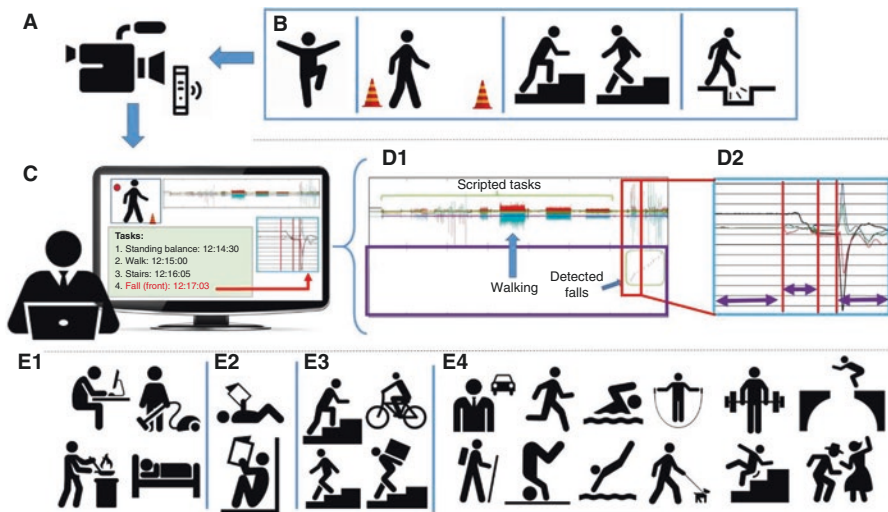
---

<sup>3</sup>These data will be stored as metadata describing and giving information about the IMU sensor data.

<sup>4</sup>Usually, the fall will be predefined by a protocol. Development work will involve static falls, that is, fall from a standing position with variations in how the volunteer falls. Additionally, protocols may ask the volunteer to simulate a trip, near fall or fall during a walking task or fall when arising from a chair to mimic a real-world, free-living fall event.

and (ii) the output of the fall algorithm to verify it successfully detected a fall event from the same data (Fig. 22.4).

Use of video recording is key to help IMU system accuracy, but often is less practical outside a lab. Studies often compare the development of IMUs to *gold standards* but fail to recognize the fundamental differences between systems or the inherent error associated with all electronics-based systems [13]. Regardless of video capture frequencies, video is currently the best standard as it can categorically and definitively record exact sequence of activities as well as provide the environmental context relating to the fall events. This is something IMU data cannot yet comprehensively provide due to the lack of real-world (free-living) fall studies involving robust algorithm deployment for all aspects of movement in all environments. However, recent developments have begun to use IMU data with complex machine-learning



**Fig. 22.4** The use of wearables with a camcorder (A) is standard validation processes within laboratory testing. Typically, the participant will perform a number of predefined tasks (B; e.g., standing balance, walking between fixed points). Usually, these are performed by young and older adults as they are deemed safe. The former usually perform falls in laboratories only to avoid risk of injury. Falls may usually be onto soft surfaces with participants under instruction to protect themselves (arms outstretched) to ensure safety, but this can compromise algorithm accuracy and is not representative of real-world fall events. A trained researcher will analyse wearable (IMU) and video data to ensure the automated recognition of falls are detected after or during scripted tasks (depending on the order of the protocol). The researcher will examine the algorithm output (D1) and often the raw IMU data (D2). Generally, laboratory protocols will replicate as many activities of daily life (ADLs) as possible (E1, e.g., sitting working at a desk, cleaning). However, people generally do not sit or lay on a bed in a laboratory like they do in habitual environments (E2), making real-world ADL and fall classification very difficult. Complex ADLs such as stair ascent/descent, or dynamic seating and standing activities need to be considered for algorithm accuracy (E3). That extends to other more energetic activities including various forms of exercise, carrying loads, near falls (trips), jumping and even dancing (E4). Icons by Adioma (<https://adioma.com/>) and ShareIcon ([www.shareicon.net](http://www.shareicon.net))

algorithms to achieve that goal [52]. For now, multiple video deployment within the home is one suggestion but is far from ideal due to cost and burden of retrofitting equipment within a person's home. Alternatively, wearable cameras are aiding context description helping to categorize falls in the home and beyond. Yet, this is no easy or quick solution as trained observers must carefully study longitudinal recordings to categorize and label periods of activity and cross-reference with algorithm outputs. Automated video-based algorithms will help overcome this manual process but are in early stages of development and must undergo robust validation and reliability checking before used as a (gold) standard for comparison.

---

## Algorithms

### Fall Detection

Here, IMU-based fall detection algorithms are presented from early designs with a focus on the current state-of-the-art. To date, fall detection research has primarily focused on laboratory testing with young healthy volunteers performing static or simulated falls during walking or transitional-based tasks. The obvious limitation here is the use of younger adults within controlled settings trying to replicate free-living events which is unrepresentative of those who are to benefit from the research, the natural settings they reside and the range of fall-related circumstances [53]. Indeed, this is corroborated by a recent scoping review which found testing/evaluation settings are greatly different from real-life context and research should focus on evaluating technologies to detect older adult falls in free-living environments [54]. Nonetheless, developments to date have aided innovation and provided numerous methodologies to aid falls research.

### IMU – Thresholds

Early work with IMUs concentrated on the detection of a fall only. One prominent work includes the use of IMUs attached to various body locations (e.g. trunk, thigh) during eight different fall types: forward falls, backward falls and lateral falls left and right, performed with legs straight and flexed [55]. In addition, the referenced study had volunteers perform ADL (e.g. walking, transfer in/out of a car). Thresholds (cut-points) were applied to all IMU acceleration data which resulted in the trunk-based IMU better able to distinguish falls from ADL compared to the IMU on the thigh. Examples of other earlier work are shown in Table 22.1.

### IMU – Machine Learning

Although threshold-based algorithms first shed light on the utility of IMU data detecting fall-related events, they have been recently compared to complex but more

**Table 22.1** Some threshold-based fall detection algorithms

Study	IMU location	Details	Algorithm	Accuracy
Bourke et al. [55]	Tri-axial accelerometer on the trunk and thigh	Discriminated between falls and activities of daily living (ADL). Young adults ( $n = 10$ ) used for falls data but older adults ( $n = 10$ ) for ADL in own homes	Root sum of squares (RMS) calculated from each IMU. Thresholds applied to upper and lower peak accelerations UFT and LFT, respectively	Thresholds determined from examining peak accelerations during all activities. Overall: Trunk UFT = 100% <sup>a</sup> Trunk LFT = 91.3% <sup>a</sup> Thigh UFT = 83.3% <sup>a</sup> Thigh LFT = 67.1% <sup>a</sup>
Kangas et al. [56]	Tri-axial accelerometer on the waist, wrist and head (forehead)	Discriminated between falls and activities of daily living (ADL). Two young adults for falls and ADL	Used RMS (detailed as total sum vector, $SV_{TOT}$ ), difference between max and min acceleration ( $SV_{max}$ ), dynamic sum vector ( $SV_D$ ), vertical acceleration ( $Z_2$ ), velocity and posture after the fall to improve fall detection	Waist: $SV_{TOT} = 100\%^a / 100\%^b$ $SV_D = 100\%^a / 100\%^b$ $SV_{max} = 100\%^a / 100\%^b$ $Z_2 = 95\%^a / 100\%^b$ Wrist: $SV_{TOT} = 45\%^a / 100\%^b$ $SV_D = 32\%^a / 100\%^b$ $SV_{max} = 41\%^a / 100\%^b$ $Z_2 = 75\%^a / 100\%^b$ Head: $SV_{TOT} = 100\%^a / 100\%^b$ $SV_D = 100\%^a / 100\%^b$ $SV_{max} = 100\%^a / 100\%^b$ $Z_2 = 100\%^a / 100\%^b$
Bourke et al. [57]	Bi-axial gyroscope on the trunk	Distinguished between ADL and falls. Young adults ( $n = 10$ ) used for falls data but older adults ( $n = 10$ ) for ADL in own homes	Applied 3: FT1: threshold lowest recorded resultant angular velocity ( $\omega_{res}$ ) FT2: threshold resultant angular acceleration ( $\alpha_{res}$ , integrate velocity) FT3: threshold resultant change in trunk angle signal ( $\Theta_{res}$ )	Three fall thresholds combined identified 100% of falls (100% <sup>a</sup> / 100% <sup>b</sup> ) FT1 correctly identified 97.5% of ADL as non-falls (97.5% <sup>b</sup> ) Combining FT1 and FT2 obtained 99.2% <sup>b</sup>
Wang et al. [58]	Tri-axial accelerometer on the head (above the ear)	Distinguish seven acts of ADL (including jumping) from falls. Younger adults ( $n = 5$ )	Four criteria based on RMS/sum vector: 1. Sum vector (SV) of all 3 axes 2. SV of horizontal plane ( $S_h$ ) 3. Timestamp of falling body at rest ( $T_r$ ) and timestamp of initial contact with ground ( $T_{ic}$ ) 4. Backward integration of reference velocity ( $V_{max}$ )	True accuracy unclear but authors detail their experimental results as effective by precisely distinguishing the eight types of fall and seven ADL

(continued)

**Table 22.1** (continued)

Study	IMU location	Details	Algorithm	Accuracy
Li et al. [59]	Tri-axial accelerometer and tri-axial gyroscope on the chest and thigh	Distinguish ADL (e.g. walk on stairs, jump, run), falls and fall-like activities (e.g. quickly sit-down upright, sit-down reclined). Three young healthy males	Algorithm divided into three: 1. Activity intensity analysis (using RMS on chest and thigh accelerations and angular velocities) 2. Posture analysis (angle of trunk and thigh) 3. Transition analysis (intentional vs. unintentional/fall) apply thresholds to peak values of acceleration and angular velocity, chest and thigh	Authors present two special cases normally difficult to classify as ADL (from a fall) but distinguishable using their method/system 1. Sit-down fast and 2. Fall on stairs Generally accuracies 91% <sup>a</sup> /92% <sup>b</sup> for ADL and fall detection, respectively

<sup>a</sup>Sensitivity<sup>b</sup>Specificity

adaptable machine-learning (ML) algorithms. The latter can be simply defined as methodologies to enable a computer (or IMU internal processing hardware) to automatically detect a fall if given a set of training data from which to learn what falls data are. The comparison study found that the performance of the ML algorithms was greater compared to thresholds. Specifically, the study investigated logistic regression, decision tree, Naïve Bayes, K-nearest neighbour and support vector machines with the latter providing the highest combination of sensitivity and specificity [32].

Additionally, Khan and colleagues [60] combined ML and data mining methodology, Hidden Markov Model. However, the authors introduce an added dimensionality to model unseen fall events within the Hidden Markov Model, which they describe as X-factor. This is derived from previous work to deal with un-modelled variations from normal events that may not have been analysed [61]. Thus, Khan et al. proposed the recognition of falls by observing normal ADL only with no training data. This approach is particularly insightful where the robust detection and classification of real fall data are sparse or unavailable and once detected incrementally adapts and updates its parameters to improve performance. However, the approach needs more stringent investigation as it was investigated with open datasets on younger adults in semi-structured testing situations [60]. Of note, was the collection of data from a smartphone, which often contain the same inertial sensors as generic IMUs. Smartphones are an important tool in wearable and fall research as they come readymade with the additional technologies for onwards integration of data to communication frameworks. Although most smartphones are powerful



enough to process data, one recent example offloads/transmits data to a computer as it investigates numerous ML algorithms for ADL and fall analysis [62]. In fact, this example highlights the need for algorithms to be combined. Given the complexity of real-world data collection but diversity and richness of wearable/IMU algorithms, they must be used jointly to aid free-living fall research as fall-based IMUs are hampered by a lack of accuracy. In fact, this was previously suggested but not yet widely implemented [63].

## IMU – Fusion

The ability of IMUs to gather data to inform many human movement-related activities has been previously highlighted. Thus, fusing or implementing different algorithms on the same data can provide more informed activity recognition that may lead to a fall. Typically, gait research has aligned to use a single IMU on the lower back to capture a range of micro gait outcomes, sensitive to ageing and pathology [64–66]. This led to the investigation of gait and falls from IMU data at the same location, showing a reduced number of false positives (false fall detection events) by understanding the broader activities performed [67]. Similarly, ML algorithms and smartphones have been used to help characterize walking patterns and falls. Approaches such as these highlight how a combination of traditional and/or more novel approaches can help improve fall detection rates while showing holistic use of IMUs for various outcomes. If algorithms cannot be fused, fall detection knowledge may also be supplemented by data fusion approaches through ubiquitous sensing. However, significant technology integration challenges exist within that field [68].

## IMU and Video

Of course, data and algorithm fusion extends to IMU and video. Algorithms from the latter are quite complex given the heterogeneity of, for example, scenes and lighting conditions that are captured within free-living environments. Feature extraction to aid fall detection in new and cluttered environments is difficult, and continuously gathering video data significantly affects memory and battery capabilities for all wearables. Recent work fused video from a smartphone (worn at the waist) and its embedded inertial sensors to create a robust and reliable fall detection algorithm [43]. Although the study achieved high sensitivity and specificity (>90%) during basic scripted tasks with a generic video recorder and a low number of false positives with the smartphone during more complex ADLs, it estimated a use time of less than 5 h. Here, suggestions to improve/extend battery life include using the accelerometer (IMU) data only to continuously sample movement (uses less battery and memory) and once detected, switching the camera to record. That would greatly limit video data and extend smartphone recording capabilities.

## Fall Prediction

### Gait

The ability to predict falls has obvious implications for patient care and is the focus of instrumented gait assessment. As previously discussed, the ability to robustly quantify gait with a single IMU is achievable, as well as its longitudinal deployment in free-living to investigate habitual micro characteristics in comparison to clinical/laboratory settings with arguments to target the former as the optimal environment for more informed patient assessment [69]. Although the best predictor is falls history, it would be ideal to ensure the patient does not experience any fall. To date, numerous studies investigated wearable-based predictive models, including combination with clinical assessments and showed enhanced fall-risk prediction compared to clinical assessment only [70–72].

### Sway

IMUs have shown utility to capture even discrete human movement, body/postural sway during periods of standing [73]. In fact, recent work suggests this approach should be the preferred method of assessing postural sway (for vestibular function) during standing balance tests across the age continuum [74]. In short, recent work has shown IMU-based outcomes can reliably estimate balance impairment and associated fall risk [75] when compared to a traditional method<sup>5</sup> during solitary or repeated testing scenarios [76]. Moreover, work is extending postural sway assessment beyond standing to dynamic balance (during gait) where novel IMU outcomes like root mean square (RMS) of acceleration are complimenting best practise outcomes such as step width or step length [77]. Complementing new with well-known outcomes is key to understanding how the former can add pragmatic insight to daily clinical practise. It is important newly derived outcomes remain tethered/grounded to established conceptual models [78], ensuring translation from engineering to medical professionals and uptake by the latter.

### Near Falls

Although fall detection is of utmost importance to ensure the continuing health and safety of those at risk of falling [55], the ability to detect near falls or predict them before they occur is of growing interest. The latter can target physiotherapy-based strategies such as muscle strengthening exercises to avoid injury [79]. Yet, falls are difficult to quantify with traditional patient self-report often grossly underestimate the number of falls experienced. This is hampered by the variation of how falls are defined with efforts to standardize falls classification through self-report [79]. The referenced study presents a simplified classification defined by transitional,

---

<sup>5</sup> Berg Balance Scale

combined and advanced falls where the latter identifies complex high-risk motor tasks with significant environmental challenges, for example, hill walking. It is reasonable to assume that near falls are more likely to occur in this situation resulting in a trip, slip, misstep or loss of balance. Near falls with wearables was systematically reviewed by Pang et al. and found insufficient evidence to determine that near falls can be accurately detected and distinguished from actual falls and ADLs in older adults ( $> 60$  years). However, it was found that laboratory-induced near falls can be distinguished from actual falls and other ADLs in younger adults ( $< 30$  years). The authors concluded that there is a dearth of large, high-quality studies investigating near falls with wearables in real-life settings with older people [80].

---

## Brief Case Studies

### Parkinson's Disease

Falls are prevalent in pathological cohorts but notably Parkinson's disease (PD) where recent work has expertly examined the use of wearables and associated technologies where notable opportunities exist [7, 81–84]. However, perhaps due to wearable fall system heterogeneity, it is recognized that a gold standard for fall risk detection remains a major unmet need [85]. Although self-report (diaries) are subjective with high attrition rates [86], they remain 'state of the art' (i.e. simple but effective).

The role of algorithm/data fusion becomes clear within PD when considering the spectrum of motor-related disease characteristics, for example, bradykinesia, shuffling gait and slow ADL [87]. Of additional note is freezing of gait (FOG). That affects the legs during walking, manifested as a sudden and temporary inability to move [87] that may result in a fall. Current stand-alone technological efforts on this topic utilize deep learning (ML methodology) in a home environment to achieve high FOG detection accuracies [88] but should complement other approaches of assessment [89–92] for more rounded technology development in this field. Interestingly, eye-tracking technology recently provided evidence for route pre-viewing as a potential intervention to reduce risk of tripping and falling in older adults [93]. Although replication of those findings within PD is difficult due to visuo-cognitive challenges [94], recommendations were made for the composite use of instruments to achieve reliability and validity of visual sampling outcomes but that (again) is hindered by a lack of standardization [95].

### European Projects

A few European fall-related projects have recently come to completion. Here, descriptions and general findings of two prominent collaborations are given, representing the latest in large multi-disciplinary projects networking across several borders.

**Table 22.2** FARSEEING work packages

Project management (WP1)
User perspectives and psychological aspects about ICT technologies for ‘ageing well’ (WP2)
Technological development (WP3)
Implementation and operational validation of longitudinal monitoring of mobility to early predict mobility disability and falls (WP4)
Tele-medical service models (WP5)
Knowledge acquisition, consolidation and generalization about falls through a meta-database (WP6)
Designing and testing a complex/self-adaptive intervention to reduce fall risks (WP7)
Dissemination (WP8)
Business models (WP9)

**FARSEEING<sup>6</sup>**

This included ten partners across five countries and aimed to improve fall identification, prediction and prevention. There was a focus on information and communications technology devices and the opportunities they can provide to support older adults in their own environment. The project was divided across nine work packages (WP) with different partners leading on each (Table 22.2).

Readers are directed to the project website for full publication listings, but two papers are highlighted here that may interest readers. The first compared self-recovered falls and non-recovered falls with long lies, examining frequency of unrecovered falls and resting duration [96]. This study also provided some useful algorithm development insights such as updating the assumption that a horizontal trunk position classifies a resting phase. The authors found that fallers with long lying periods often attempted to stand or adopt upright sitting positions but were not adequate to facilitate a successful recovery to a standing position. New insights such as this were possible due to a rich IMU-based database collected during the project. Currently, a dataset of 20 selected fall events is now available for researchers on request which may be useful for those developing algorithms but with little or no access to patient recruitment.<sup>7</sup> The second FARSEEING study of interest relates to the development of a taxonomy of technologies to classify and characterize components of falls-related studies and interventions. Specifically, the taxonomy is a tool detailing a common language and classification system to standardize the approach to reporting studies in the fields of biomedical informatics and fall prevention [97]. The latter study is vital to ensure the field moves in a co-ordinated and linear manner where consistency is key.

<sup>6</sup>FARSEEING: FALL Repository for the design of Smart and sELf-adaptive Environments prolonging Independent living: <http://farseeingresearch.eu/>

<sup>7</sup><http://farseeingresearch.eu/the-farseeing-real-world-fall-repository-a-large-scale-collaborative-database-to-collect-and-share-sensor-signals-from-real-world-falls>

## V-Time<sup>8</sup>

This randomized controlled trial aimed to evaluate two walking interventions to reduce fall incidences while improving walking, balance and cognition. A 6-week treadmill training programmed augmented by virtual reality was compared with a conventional treadmill training programme. Three hundred participants across three cohorts in five clinical centres across Europe were recruited: older adults who fall with and without mild cognitive impairments (MCI) and people with PD who fall [98]. The primary outcome of the study was fall rate, quantified by falls diary/calendar post-intervention where a fall was defined with the recommendations Prevention of Falls Network Europe.<sup>9</sup> Gait, balance and a range of other outcomes were also collected [98]. RCT findings showed that in a diverse group of those at high risk for falls, treadmill training with virtual reality led to reduced fall rates [99].

---

## Remote Monitoring: The Great Beyond

Only when common currency exists between wearables (including outcomes) will they be suitable for onwards integration to communal communication frameworks, currently defined by the Internet of Things (IoT).

## The IoT

Developments for relay of fall-related detection currently consider IoT functionality, creation of real-time warning systems alerting a carer or medical service. Currently, work focuses on improving energy efficiency of wearables and associated technologies [100]. Additionally, other work implements a pre-fall detection IoT system, detecting human falls approximately 250 milliseconds before it occurs [101]. The purpose of the latter methodology is to integrate into wearable airbag systems to protect the faller before impact with the ground.<sup>10</sup>

## Big Data

Use of any wearable facilitates the collection of data, lots and lots of data. This can be a double-edged sword. The collection of big data provides opportunities for in-depth patient analysis but the proliferation of information, which many healthcare professionals may struggle to deal with or understand within the context of current patient care pathways [102]. How big is big? Consider an IMU with a tri-axial accelerometer only, sampling continuously at 100 Hz for 7 days (the norm). That is

---

<sup>8</sup>[https://cordis.europa.eu/project/rcn/101785\\_en.html](https://cordis.europa.eu/project/rcn/101785_en.html)

<sup>9</sup>ProFaNE: [www.profane.eu.org](http://www.profane.eu.org)

<sup>10</sup>E.G. <https://activeprotective.com/>

three channels (tri-axial) at 100 data points/second each for 24 hours/day for 7 days which equates to >181 million data points. This is increased by repeated testing (follow-up), making data management key for wearable studies. Thus, the robust/accurate detection of a single or even multiple near fall or fall event(s) is extremely difficult, but understanding the volume, variety, velocity and veracity of big data is key [103]. Yet, data sharing between research groups and/or commercial systems to promote integration into health information systems is currently lacking [104]. This is of importance where pooling of diverse data sets (e.g. interviews, family histories, muscle strength, bioelectrical impedance, blood and urine assays) can play a key role in the development of fall prediction tools [105].

## Validation and Verification

Innovation is rife with wearable research. The novelty of devices, their application in various cohorts and coding of algorithms make this an exciting and constantly evolving field. Yet, the abundance of creation is leading to heterogeneous development, where established and emerging groups are competing to create the next wearable-based diagnostic. Many recent literature reviews conclude that the field needs to be harmonized with the creation of standardized protocols for wearable design, validation, verification and reliability testing [51, 54, 106]. This extends to the description of studies including wearable outcomes,<sup>11</sup> where the richness of data means it can be analysed and presented in a plethora of ways [28, 51, 54, 107]. In short, innovation supply often exceeds pragmatic demand, but in order to maximize the benefit of these new technological advances it requires greater synergy between clinical need and opportunity and technological opportunity.

---

## References

1. Montero-Odasso M, Speechley M. Falls in cognitively impaired older adults: Implications for risk assessment and prevention. *J Am Geriatr Soc*, in print.
2. World Health Organization. Falls. 2018. [Online]. Available: <http://www.who.int/mediacentre/factsheets/fs344/en/>.
3. Sakurai R, Fujiwara Y, Yasunaga M, Suzuki H, Sakuma N, Imanaka K, Montero-Odasso M. Older adults with fear of falling show deficits in motor imagery of gait. *J Nutr Health Aging*. 2017;21(6):721–6.
4. Godfrey A, Conway R, Meagher D, OLaighin G. Direct measurement of human movement by accelerometry. *Med Eng Phys*. 2008;30(10):1364–86.
5. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. *Maturitas*. 2013;75(1):51–61.
6. Rice LA, Ousley C, Sosnoff JJ. A systematic review of risk factors associated with accidental falls, outcome measures and interventions to manage fall risk in non-ambulatory adults. *Disabil Rehabil*. 2015;37(19):1697–705.

---

<sup>11</sup> For gait and falls but extends to all aspects of wearable measurement

7. Del Din S, Godfrey A, Mazza C, Lord S, Rochester L. Free-living monitoring of Parkinson's disease: lessons from the field. *Mov Disord*. 2016;31(9):1293–313.
8. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research and policy implications of a core geriatric concept. *J Am Geriatr Soc*. 2007;55(5):780–91.
9. Thurston AJ. Pare and prosthetics: the early history of artificial limbs. *ANZ J Surg*. 2007;77(12):1114–9.
10. Finch JL, Heath GH, David AR, Kulkarni J. Biomechanical assessment of two artificial big toe restorations from ancient Egypt and their significance to the history of prosthetics. *J Prosthet Orthot*. 2012;24(4):181–91.
11. Gerzeli S, Torbica A, Fattore G. Cost utility analysis of knee prosthesis with complete micro-processor control (c-leg) compared with mechanical technology in trans-femoral amputees. *Eur J Health Econ*. 2009;10(1):47–55.
12. Highsmith MJ, Kahle JT, Bongiorno DR, Sutton BS, Groer S, Kaufman KR. Safety, energy efficiency, and cost efficacy of the c-leg for transfemoral amputees: a review of the literature. *Prosthetics Orthot Int*. 2010;34(4):362–77.
13. Richards J, Payne K, Myatt D, Chohan A. Do orthotic walkers affect knee and hip function during gait? *Prosthetics Orthot Int*. 2016;40(1):137–41.
14. Choi H-J, Ko C-Y, Kang S, Ryu J, Mun M, Jeon H-S. Effects of balance ability and handgrip height on kinematics of the gait, torso, and pelvis in elderly women using a four-wheeled walker. *Geriatr Gerontol Int*. 2015;15(2):182–8. <https://doi.org/10.1111/ggi.12246>
15. Schüle S, Barth J, Rampp A, Rupprecht R, Eskofier BM, Winkler J, Gaßmann K-G, Klucken J. Instrumented gait analysis: a measure of gait improvement by a wheeled walker in hospitalized geriatric patients. *J NeuroEng Rehabil*. 2017;14(1):18.
16. Lim CD, Wang C-M, Cheng C-Y, Chao Y, Tseng S-H, Fu L-C. Sensory cues guided rehabilitation robotic walker realized by depth image-based gait analysis. *IEEE Trans Autom Sci Eng*. 2016;13(1):171–80.
17. Tan AM, Fuss FK, Weizman Y, Woudstra Y, Troynikov O. Design of low cost smart insole for real time measurement of plantar pressure. *Procedia Technol*. 2015;20:117–22.
18. Wu Y, Xu W, Liu JJ, Huang M-C, Luan S, Lee Y. An energy-efficient adaptive sensing framework for gait monitoring using smart insole. *IEEE Sensors J*. 2015;15:2335.
19. Lin F, Wang A, Zhuang Y, Tomita MR, Xu W. Smart insole: a wearable sensor device for unobtrusive gait monitoring in daily life. *IEEE Trans Ind Inform*. 2016;12(6):2281–91.
20. Zoss AB, Kazerooni H, Chu A. Biomechanical design of the Berkeley lower extremity exoskeleton (BLEEX). *IEEE/ASME Trans Mechatron*. 2006;11(2):128–38.
21. Veneman JF, Kruidhof R, Hekman EEG, Ekkelenkamp R, Asseltonk EHFV, van der Kooij H. Design and evaluation of the LOPES exoskeleton robot for interactive gait rehabilitation. *IEEE Trans Neural Syst Rehabil Eng*. 2007;15(3):379–86.
22. Bortole M, Venkatakrishnan A, Zhu F, Moreno JC, Francisco GE, Pons JL, Contreras-Vidal JL. The H2 robotic exoskeleton for gait rehabilitation after stroke: early findings from a clinical study. *J NeuroEng Rehabil*. 2015;12(1):54.
23. Belda-Lois J-M, Mena-del Horno S, Bermejo-Bosch I, Moreno JC, Pons JL, Farina D, Iosa M, Molinari M, Tamburella F, Ramos A, Caria A, Solis-Escalante T, Brunner C, Rea M. Rehabilitation of gait after stroke: a review towards a top-down approach. *J NeuroEng Rehabil*. 2011;8(1):66.
24. del Ama AJ, Gil-Agudo Á, Pons JL, Moreno JC. Hybrid FES-robot cooperative control of ambulatory gait rehabilitation exoskeleton. *J NeuroEng Rehabil*. 2014;11(1):27.
25. Ambrosio F, Wolf SL, Delitto A, Fitzgerald GK, Badyak SF, Boninger ML, Russell AJ. The emerging relationship between regenerative medicine and physical therapeutics. *Phys Ther*. 2010;90(12):1807–14. <https://doi.org/10.2522/ptj.20100030>.
26. Willett NJ, Li M-TA, Uhrig BA, Boerckel JD, Huebsch N, Lundgren TS, Warren GL, Guldberg RE. Attenuated human bone morphogenetic protein-2-mediated bone regeneration in a rat model of composite bone and muscle injury. *Tissue Eng Part C Methods*. 2013;19(4):316–25.
27. Sejdic E, Millecamps A, Teoli J, Rothfuss MA, Franconi NG, Perera S, Jones AK, Brach JS, Mickle MH. Assessing interactions among multiple physiological systems during walk-



- ing outside a laboratory: an android based gait monitor. *Comput Methods Prog Biomed.* 2015;122(3):450–61.
28. Godfrey A. Wearables for independent living in older adults: gait and falls. *Maturitas.* 2017;100:16–26.
29. Tedesco S, Barton J, O'Flynn B. A review of activity trackers for senior citizens: Research perspectives, commercial landscape and the role of the insurance industry. *Sensors.* 2017;17(6).
30. Nyan MN, Tay FEH, Murugasu E. A wearable system for pre-impact fall detection. *J Biomech.* 2008;41(16):3475–81.
31. Paoli R, Fernandez-Luque FJ, Domenech G, Martinez F, Zapata J, Ruiz R. A system for ubiquitous fall monitoring at home via a wireless sensor network and a wearable mote. *Expert Syst Appl.* 2012;39(5):5566–75.
32. Aziz O, Musngi M, Park EJ, Mori G, Robinovitch SN. A comparison of accuracy of fall detection algorithms (threshold-based vs. machine learning) using waist-mounted tri-axial accelerometer signals from a comprehensive set of falls and non-fall trials. *Med Biol Eng Comput.* 2017;55(1):45–55.
33. Tamura T, Yoshimura T, Sekine M, Uchida M, Tanaka O. A wearable airbag to prevent fall injuries. *IEEE Trans Inf Technol Biomed.* 2009;13(6):910–4.
34. Aziz O, Robinovitch SN. An analysis of the accuracy of wearable sensors for classifying the causes of falls in humans. *IEEE Trans Neural Syst Rehabil Eng.* 2011;19(6):670–6.
35. Aziz O, Park EJ, Mori G, Robinovitch SN. Distinguishing the causes of falls in humans using an array of wearable tri-axial accelerometers. *Gait Posture.* 2014;39(1):506–12.
36. Ozdemir AT, Barshan B. Detecting falls with wearable sensors using machine learning techniques. *Sensors.* 2014;14(6):10691–708.
37. Pierleoni P, Belli A, Palma L, Pellegrini M, Pernini L, Valenti S. A high reliability wearable device for elderly fall detection. *IEEE Sensors J.* 2015;15(8):4544–53.
38. Mohler M, Wendel C, Taylor-Piliae R, Toosizadeh N, Najafi B. Motor performance and physical activity as predictors of prospective falls in community-dwelling older adults by frailty level: application of wearable technology. *Gerontology.* 2016;62(6):654–64.
39. Khan SS, Taati B. Detecting unseen falls from wearable devices using channel-wise ensemble of autoencoders. *Expert Syst Appl.* 2017;87:280–90.
40. Gia TN, Sarker VK, Tcareno I, Rahmani AM, Westerlund T, Liljeberg P, Tenhunen H. Energy efficient wearable sensor node for IoT-based fall detection systems. *Microprocess Microsyst.* 2018;56:34–46.
41. Bianchi F, Redmond SJ, Narayanan MR, Cerutti S, Lovell NH. Barometric pressure and triaxial accelerometry-based falls event detection. *IEEE Trans Neural Syst Rehabil Eng.* 2010;18(6):619–27.
42. Casilari E, Oviedo-Jimenez MA. Automatic fall detection system based on the combined use of a smartphone and a smartwatch. *PLoS One.* 2015;10(11):1–11.
43. Ozcan K, Velipasalar S. Wearable camera- and accelerometer-based fall detection on portable devices. *IEEE Embed Syst Lett.* 2016;8(1):6–9.
44. Patel S, Park H, Bonato P, Chan L, Rodgers M. A review of wearable sensors and systems with application in rehabilitation. *J NeuroEng Rehabil.* 2012;9(1):21.
45. Paradiso R, Loriga G, Taccini N. A wearable health care system based on knitted integrated sensors. *IEEE Trans Inf Technol Biomed.* 2005;9(3):337–44.
46. Sejdic E, Lowry KA, Bellanca J, Redfern MS, Brach JS. A comprehensive assessment of gait accelerometry signals in time, frequency and time-frequency domains. *IEEE Trans Neural Syst Rehabil Eng.* 2014;22(3):603–12.
47. Millecamps A, Lowry KA, Brach JS, Perera S, Redfern MS, Sejdic E. Understanding the effects of pre-processing on extracted signal features from gait accelerometry signals. *Comput Biol Med.* 2015;62:164–74.
48. Lowe SA, O'Laughlin G. Monitoring human health behaviour in one's living environment: a technological review. *Med Eng Phys.* 2014;36(2):147–68.
49. Godfrey A, Lara J, Del Din S, Hickey A, Munro CA, Wiuff C, Chowdhury SA, Mathers JC, Rochester L. Icap: instrumented assessment of physical capability. *Maturitas.* 2015;82(1):116–22.

50. Lucivero F, Prainsack B. The lifestylisation of healthcare? 'Consumer genomics' and mobile health as technologies for healthy lifestyle. *Appl Trans Genom.* 2015;4:44–9.
51. Kekade S, Hsieh C-H, Islam MM, Atique S, Mohammed Khalfan A, Li Y-C, Abdul SS. The usefulness and actual use of wearable devices among the elderly population. *Comput Methods Prog Biomed.* 2018;153:137–59.
52. Hu B, Dixon PC, Jacobs JV, Dennerlein JT, Schiffman JM. Machine learning algorithms based on signals from a single wearable inertial sensor can detect surface- and age-related differences in walking. *J Biomech.* 2018;71:37.
53. Crenshaw JR, Bernhardt KA, Achenbach SJ, Atkinson EJ, Khosla S, Kaufman KR, Amin S. The circumstances, orientations, and impact locations of falls in community-dwelling older women. *Arch Gerontol Geriatr.* 2017;73:240–7.
54. Lapierre N, Neubauer N, Miguel-Cruz A, Rios Rincon A, Liu L, Rousseau J. The state of knowledge on technologies and their use for fall detection: a scoping review. *Int J Med Inform.* 2018;111:58–71.
55. Bourke AK, O'Brien JV, Lyons GM. Evaluation of a threshold-based tri-axial accelerometer fall detection algorithm. *Gait Posture.* 2007;26(2):194–9.
56. Kangas M, Konttila A, Winblad I, Jamsa T. "Determination of simple thresholds for accelerometry-based parameters for fall detection," 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS 2007); 2007. p. 1367–70.
57. Bourke AK, Lyons GM. A threshold-based fall-detection algorithm using a bi-axial gyroscope sensor. *Med Eng Phys.* 2008;30(1):84–90.
58. Wang CC, Chiang CY, Lin PY, Chou YC, Kuo IT, Huang CN, Chan CT. Development of a fall detecting system for the elderly residents. In: 2008 2nd International Conference on Bioinformatics and Biomedical Engineering: Conference Proceedings; 2008. p. 1359–62.
59. Li Q, Stankovic JA, Hanson MA, Barth AT, Lach J, Zhou G. Accurate, fast fall detection using gyroscopes and accelerometer-derived posture information. In: 2009 Sixth International Workshop on Wearable and Implantable Body Sensor Networks: Conference Proceedings; 2009. p. 138–43.
60. Khan SS, Karg ME, Kulic D, Hoey J. Detecting falls with X-factor hidden Markov models. *Appl Soft Comput.* 2017;55:168–77.
61. Quinn JA, Williams CKI, McIntosh N. Factorial switching linear dynamical systems applied to physiological condition monitoring. *IEEE Trans Pattern Anal Mach Intell.* 2009;31(9):1537–51.
62. Hakim A, Huq MS, Shanta S, Ibrahim BSKK. Smartphone based data mining for fall detection: analysis and design. *Procedia Comput Sci.* 2017;105:46–51.
63. Noury N, Fleury A, Rumeau P, Bourke AK, Laighin GO, Rialle V, Lundy JE. Fall detection - principles and methods. In: 29th Annual International Conference of the IEEE Engineering in Medicine and Biology Society: Conference Proceedings; 2007. p. 1663–6.
64. Lord S, Galna B, Verghese J, Coleman S, Burn D, Rochester L. Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach. *J Gerontol Series A.* 2013;68(7):820–7.
65. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, Lipton RB. Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc.* 2008;56(7):1244–51.
66. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. *J Neurol Neurosurg Psychiatry.* 2007;78(9):929–35.
67. Godfrey A, Bourke A, Din SD, Morris R, Hickey A, Helbostad JL, Rochester L. Towards holistic free-living assessment in Parkinson's disease: Unification of gait and fall algorithms with a single accelerometer. In: Proceeding of the 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). Orlando, FL, USA; 2016. p. 651–4.
68. King RC, Villeneuve E, White RJ, Sherratt RS, Holderbaum W, Harwin WS. Application of data fusion techniques and technologies for wearable health monitoring. *Med Eng Phys.* 2017;42:1–12.
69. Del Din S, Godfrey A, Galna B, Lord S, Rochester L. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. *J NeuroEng Rehabil.* 2016;13(1):46.

70. Howcroft J, Kofman J, Lemaire ED. Prospective fall-risk prediction models for older adults based on wearable sensors. *IEEE Trans Neural Syst Rehabil Eng.* 2017;25(10):1812–20.
71. Weiss A, Brozgol M, Dorfman M, Herman T, Shema S, Giladi N, Hausdorff JM. Does the evaluation of gait quality during daily life provide insight into fall risk? A novel approach using 3-day accelerometer recordings. *Neurorehabil Neural Repair.* 2013;27(8):742–52.
72. van Schooten KS, Pijnappels M, Rispens SM, Elders PJ, Lips P, van Dieën JH. Ambulatory fall-risk assessment: amount and quality of daily-life gait predict falls in older adults. *J Gerontol A Biol Sci Med Sci.* 2015;70(5):608–15.
73. Mancini M, Salarian A, Carlson-Kuhta P, Zampieri C, King L, Chiari L, Horak FB. Isway: a sensitive, valid and reliable measure of postural control. *J Neuroeng Rehabil.* 2012;9:59.
74. Rine RM, Schubert MC, Whitney SL, Roberts D, Redfern MS, Musolino MC, Roche JL, Steed DP, Corbin B, Lin CC, Marchetti GF, Beaumont J, Carey JP, Shepard NP, Jacobson GP, Wrisley DM, Hoffman HJ, Furman G, Slotkin J. Vestibular function assessment using the NIH toolbox. *Neurology.* 2013;80(11 Suppl 3):S25–31.
75. Shahzad A, Ko S, Lee S, Lee JA, Kim K. Quantitative assessment of balance impairment for fall-risk estimation using wearable triaxial accelerometer. *IEEE Sensors J.* 2017;17(20):6743–51.
76. Mahoney JR, Oh-Park M, Ayers E, Verghese J. Quantitative trunk sway and prediction of incident falls in older adults. *Gait Posture.* 2017;58:183–7.
77. Peebles AT, Bruetsch AP, Lynch SG, Huisinga JM. Dynamic balance in persons with multiple sclerosis who have a falls history is altered compared to non-fallers and to healthy controls. *J Biomech.* 2017;63:158–63.
78. Lord S, Galna B, Rochester L. Moving forward on gait measurement: toward a more refined approach. *Mov Disord.* 2013;28(11):1534–43.
79. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev.* 2012;9(11).
80. Pang I, Okubo Y, Sturnieks D, Lord SR, Brodie MA. Detection of near falls using wearable devices: a systematic review. *J Geriatr Phys Ther.* 2018, in press.
81. Kubota KJ, Chen JA, Little MA. Machine learning for large-scale wearable sensor data in Parkinson's disease: concepts, promises, pitfalls, and futures. *Mov Disord.* 2016;31(9):1314–26.
82. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, Eskofier BM, Merola A, Horak F, Lang AE, Reilmann R, Giuffrida J, Nieuwboer A, Home M, Little MA, Litvan I, Simuni T, Dorsey ER, Burack MA, Kubota K, Kamondi A, Godinho C, Daneault J-F, Mitsi G, Krinke L, Hausdorff JM, Bloem BR, Papapetropoulos S, T. on behalf of the Movement Disorders Society Task Force on. Technology in Parkinson's disease: Challenges and opportunities. *Mov Disord.* 2016;31(9):1272–82.
83. Sanchez-Ferro A, Elshehabi M, Godinho C, Salkovic D, Hobert MA, Domingos J, van Uem JMT, Ferreira JJ, Maetzler W. New methods for the assessment of Parkinson's disease (2005 to 2015): a systematic review. *Mov Disord.* 2016;31(9):1283–92.
84. Godinho C, Domingos J, Cunha G, Santos AT, Fernandes RM, Abreu D, Goncalves N, Matthews H, Isaacs T, Duffen J. A systematic review of the characteristics and validity of monitoring technologies to assess Parkinson's disease. *J Neuroeng Rehabil.* 2016;13(1):24.
85. Fasano A, Canning CG, Hausdorff JM, Lord S, Rochester L. Falls in Parkinson's disease: a complex and evolving picture. *Mov Disord.* 2017;32(11):1524–36.
86. Hunter H, Rochester L, Morris R, Lord S. Longitudinal falls data in Parkinson's disease: feasibility of fall diaries and effect of attrition. *Disabil Rehabil.* 2017:1–6.
87. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry.* 2008;79(4):368–76.
88. Camps J, Sama A, Martin M, Rodriguez-Martin D, Perez-Lopez C, Arostegui JMM, Cabestany J, Catala A, Alcaine S, Mestre B, Prats A, Crespo-Maraver MC, Counihan TJ, Browne P, Quinlan LR, Laighin GO, Sweeney D, Lewy H, Vainstein G, Costa A, Annicchiarico R, Bayes A, Rodriguez-Molinero A. Deep learning for freezing of gait detection in Parkinson's disease patients in their homes using a waist-worn inertial measurement unit. *Knowl-Based Syst.* 2018;139:119–31.

89. LeMoyne R, Mastroianni T, Cozza M, Coroian C, Grundfest W. Implementation of an iPhone for characterizing Parkinson's disease tremor through a wireless accelerometer application. In: *Proceeding of the 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Buenos Aires, Argentina: IEEE, Conference Proceedings; 2010. p. 4954–8.
90. Lin Z, Dai H, Xiong Y, Xia X, Horng SJ. Quantification assessment of bradykinesia in Parkinson's disease based on a wearable device. In: *39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC): Conference Proceedings*; 2017. p. 803–6.
91. Cai G, Huang Y, Luo S, Lin Z, Dai H, Ye Q. Continuous quantitative monitoring of physical activity in Parkinson's disease patients by using wearable devices: a case-control study. *Neurol Sci*. 2017;38(9):1657–63.
92. Dontje ML, de Greef MH, Speelman AD, van Nimwegen M, Krijnen WP, Stolk RP, Kamsma YP, Bloem BR, Munneke M, van der Schans CP. Quantifying daily physical activity and determinants in sedentary patients with Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(10):878–82.
93. Curzon-Jones BT, Hollands MA. Route previewing results in altered gaze behaviour, increased self-confidence and improved stepping safety in both young and older adults during adaptive locomotion. *Exp Brain Res*. 2018:1–13.
94. Stuart S, Lord S, Hill E, Rochester L. Gait in Parkinson's disease: a visuo-cognitive challenge. *Neurosci Biobehav Rev*. 2016;62:76–88.
95. Stuart S, Alcock L, Galna B, Lord S, Rochester L. The measurement of visual sampling during real-world activity in Parkinson's disease and healthy controls: a structured literature review. *J Neurosci Methods*. 2014;222:175–88.
96. Schwickert L, Klenk J, Zijlstra W, Forst-Gill M, Sczuka K, Helbostad JL, Chiari L, Aminian K, Todd C, Becker C. Reading from the black box: what sensors tell us about resting and recovery after real-world falls. *Gerontology*. 2018;64(1):90–5.
97. Boulton E, Hawley-Hague H, Vereijken B, Clifford A, Guldemon N, Pfeiffer K, Hall A, Chesani F, Mellone S, Bourke A, Todd C. Developing the FARSEEING taxonomy of technologies: classification and description of technology use (including ICT) in falls prevention studies. *J Biomed Inform*. 2016;61:132–40.
98. Mirelman A, Rochester L, Reelick M, Nieuwhof F, Pelosin E, Abbruzzese G, Dockx K, Nieuwboer A, Hausdorff JM. V-TIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled trial. *BMC Neurol*. 2013;13:15.
99. Mirelman A, Rochester L, Maidan I, Del Din S, Alcock L, Nieuwhof F, Rikkert MO, Bloem BR, Pelosin E, Avanzino L, Abbruzzese G, Dockx K, Bekkers E, Giladi N, Nieuwboer A, Hausdorff JM. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. *Lancet*. 2016;388(10050):1170–82.
100. Nguyen Gia T, Sarker VK, Tcareno I, Rahmani AM, Westerlund T, Liljeberg P, Tenhunen H. Energy efficient wearable sensor node for IoT-based fall detection systems. *Microprocess Microsyst*. 2018;56:34–46.
101. Rathi N, Kakani M, El-Sharkawy M, Rizkalla M. Wearable low power pre-fall detection system with IoT and bluetooth capabilities. In: *2017 IEEE National Aerospace and Electronics Conference (NAECON): Conference Proceedings*; 2017. p. 241–4.
102. Buus-Frank M. Nurse versus machine: slaves or masters of technology? *J Obstet Gynecol Neonatal Nurs*. 1999;28(4):433–41.
103. Bellazzi R. Big data and biomedical informatics: a challenging opportunity. *Yearb Med Inform*. 2014;9:8–13.
104. Redmond SJ, Lovell NH, Yang GZ, Horsch A, Lukowicz P, Murrugarra L, Marschollek M. What does big data mean for wearable sensor systems?: contribution of the IMIA wearable sensors in healthcare WG. *Yearb Med Inform*. 2014;9(1):135–42.

105. Palumbo P, Palmerini L, Bandinelli S, Chiari L. Fall risk assessment tools for elderly living in the community: Can we do better? *PLoS One*. 2015;10(12):e0146247.
106. Sun R, Sosnoff JJ. Novel sensing technology in fall risk assessment in older adults: a systematic review. *BMC Geriatr*. 2018;18(1):14.
107. Khan SS, Hoey J. Review of fall detection techniques: a data availability perspective. *Med Eng Phys*. 2017;39:12–22.

# Index

## A

Accelerometers, 201, 404–406, 408, 409  
Activities-Specific Balance Confidence Scale (ABC), 55  
Acute coronary syndrome, 217  
Acute functional decline, 161  
Adverse drug events (ADEs), 152, 154, 156, 158–161  
Aerobic exercise, 279, 298, 300  
Age-associated striatal dopaminergic denervation (AASDD), 326  
Age-related atrophy, 294  
Age-related central nervous system changes, 165, 166  
Aging brain in cognition and mobility brain structure and function, 27–29  
 $\alpha 4\beta 2$  nicotinic cholinergic receptor, 336  
Alzheimer's disease (AD), 36, 41, 74, 77, 92, 117, 146, 211, 280, 297  
    clinical assessment, 215–217  
    falls management, 217, 218, 221  
    gait variability and fall risk in older adults, 117, 118  
    non-pharmacological interventions, 219–220  
    risk factor, 212–215  
Amantadine, 197  
Amitriptyline, 154  
Amlodipine, 157  
Amyloid-beta (Ab), 174  
Analgesic drugs, 214  
Ankle strategy, 7  
Antagonism of 5-HT<sub>6</sub> receptor, 335  
Anticholinergic activity, 328  
Anticholinergic medications, 328  
Anti-dementia drugs, 214  
Anti-hypertensive drugs, 214  
Apathy, 214  
Appropriate pharmacotherapy, 151

Artificial intelligence, 402

Assistive device, 143

## B

Beers' criteria, 156  
Behavioral symptoms, 214, 217  
Benzodiazepines, 9, 99, 154, 280  
Berg Balance Scale, 358, 381  
Berlin Aging Study (BASE), 290  
Beta-blockers, 155  
Biological ageing, 67, 70  
Biomedical informatics, 418  
Bisphosphonates, 200  
Blood oxygen level dependent (BOLD) response, 171, 172  
    fMRI, 172  
    fNIRS, 172, 173  
    neural activation and falls, measures of, 173, 174  
Body composition, 29  
Bradykinesia, 196  
Brain failure, 4  
Brain neuroimaging, 52  
Brain stress test, 8  
Brain syndromes, 4  
British National Institute for Health and Care Excellence (NICE) guidelines, 363

## C

Carbidopa, 217  
Catechol O-methyltransferase Met/Met genetic subgroup, 332  
Cautious gait, 97  
Center for Disease Control and Prevention, 273  
Center for Epidemiologic Depression Scale (CES-D), 50

- Central Benefit Model, 281, 282
- Cerebellocortical inhibition (CBI), 386
- Cholinergic brain neurons, 16
- Cholinergic denervation, 325
- Cholinergic medications, 197
- Cholinergic pharmacotherapy gait studies, 331
- Cholinergic studies in Parkinson's disease, 335
- Cholinesterase inhibitors (ChEI), 16, 17, 199, 329–331, 336
- Chronic inflammation, 74
- Ciprofloxacin, 157
- Citalopram, 154, 157
- Clinical Dementia Rating Scale, 195
- Cockcroft and Gault equation, 154
- Cognition, 4
  - cognitive enhancers, 324
  - and falls
    - executive function (EF), 58, 59
    - global, 57, 58
    - self-awareness for physical ability, 59, 60
  - gait and falls in aging, 5–6
  - improve mobility and prevent falls, 9
    - non-pharmacological interventions, 9–13
    - pharmacological interventions, 13–17
  - mobility in aging, 5
  - pathophysiology of falls, 6–9
- Cognitive-behavioral therapy, 249
- Cognitive-cognitive dual-task training studies, 297
- Cognitive deficits, 5, 17
- Cognitive distraction, 75
- Cognitive enhancers, 324
  - acetylcholine, 335
  - cognitive-motor dual-task behaviors, 324
  - etiology of falls, 323
  - executive dysfunction, 325
  - extrasynaptic acetylcholine levels, 336
  - gait, 325
  - gait worsening, 324
  - mobility impairments, 325
  - motor control, 324
  - multitasking during usual activities, 324
  - nervous system impairments, 324
  - pharmacotherapy, 334
  - risk factors, 324
  - stability, 325
  - subcortical and cortical cholinergic denervation, 325
  - synaptic acetylcholine, 336
  - therapy and falls in PD, 332, 334
- Cognitive-exercise training approaches, 17
- Cognitive frailty, 75
- Cognitively impaired older adults
  - Alzheimer's dementia, 36
  - Dementia with Lewy bodies (DLB), 37
  - epidemiology of falls, 35, 36
  - falls risk factors, 37
    - Alzheimer's dementia, 41
    - dementia with lewy bodies, 42
    - mild cognitive impairment, 41
    - Mini Mental State Examination (MMSE), 39
    - in older adults, 38
    - Parkinson's disease, 41
    - physical and cognitive functions, 39
    - posture first strategy, 39
  - gait changes, 42, 43
  - mild cognitive impairment (MCI), 36
  - Parkinson's disease (PD), 37
  - Parkinson's disease dementia, 37
- Cognitive impairment, 26, 155
  - adverse drug events in older people, 158–160
  - changes in pharmacokinetics, 153
  - dual-task (DT) training, 343, 344, 363
  - exercise
    - cognitive function and falls, 274, 275
    - falls prevention, 279, 280
    - falls risk factors, 275–277
    - mechanisms underlying falls reduction, 280–282
    - neural underpinnings, 277–279
  - injurious falls among older people, 157
  - key assessment features, 160
  - management strategies
    - acute functional decline, 161
    - manage the person, 161, 162
    - medications review, 161
  - patient factors
    - absorption, 152
    - distribution, 152, 154
    - elimination, 154, 155
    - metabolism, 154
    - pharmacodynamic changes, 155
    - pharmacokinetic changes, 152
  - potentially inappropriate medications (PIMs) (*see* Potentially inappropriate medications (PIMs))
  - prescribing cascade
    - definition, 157
    - examples of, 157
- Cognitive-motor task, 215
- Cognitive pharmacotherapy, 328, 330, 331
- Cognitive processes, 4
- Cognitive reserve (CR), 29
- Cognitive status, 358



- Cognitive training
  - in aging, 292
    - dual-task training studies in older adults, 292
    - motor responses, young and old adults, 292
    - neuroimaging, 294, 295
    - untrained tasks, transfer to, 293, 294
    - visual and verbal working memory, 292, 293
  - correlational evidence, 290
  - experimental dual-task evidence, 291
  - and mobility outcomes, 295, 297
    - computerized cognitive training, 297, 298
  - falls outcomes, 301, 302
  - multi-domain training of cognition, 298, 300, 301
  - usual gait speed, 290
- Comprehensive falls assessment
  - algorithm to guide fall assessment, 100
  - analytic clinical assessment, 99
  - causal factors, 89
  - cognition, 92
  - dual-task gait assessment, 97, 98
  - dual-task paradigm, 93
  - fall-related injuries, 100
  - falls classification, 94
  - FTSS measures, 98
  - gait, 92, 93
  - gait assessment, 95, 97
  - global cognitive functioning, 99
  - management of falls, 100
  - medication data, 99
  - precipitating factors, 89
  - predisposing factors, 89
  - sensory and motor subsystems, 100
  - severity of fall, 100
  - TUG measures, 98
  - walking aid, 100
  - walking speed, 99
- Comprehensive geriatric assessment, 161
- Comprehensive intervention programs, 364
- Computerized cognitive training, 297, 298
- Computerized tomography (CT), 168
- Confusion Assessment Method (CAM), 233
- Content-related anchoring, 347
- Continuous theta-burst stimulation (cTBS), 385
- Controlled noradrenergic clinical trials and gait/falls in PD, 333
- Cortical networks, 373
- Cortico-basal ganglia loops,
  - modulation of, 201
- Cortico-basal-ganglionic degeneration (CBGD), 191
- Culture change, 237
- D**
- Data science, 402
- Deep brain stimulation (DBS), 197, 201, 202
- Default mode network (DMN), 278
- Deficit accumulation, 69, 70, 74
- Delirium
  - clinical decision-making, 229
  - consequences of, 230
  - definition, 230
  - epidemiology, 230
  - management of, 231–233
  - prevalence of, 230
  - prevention and mobility, 252, 255
- Dementia, 4, 5, 9, 57, 76, 141, 147, 161, 195, 212, 216, 270, 274, 275, 280
- Dementia-care mapping, 249
- Dementia-related gait changes, 92
- Dementia with Lewy bodies (DLB), 37, 42, 212, 280
  - approaches to falls prevention, 200
  - DBS and non-invasive stimulation, 201, 202
  - definition, 191, 192
  - diagnosis for, 192
  - dopaminergic deficits, 192
  - epidemiology, 191–193
  - extrinsic risk modification
    - environmental assessment and modification, 201
    - new devices in fall prevention, 201
  - functional neuroanatomy and neurochemistry, 202
  - optimizing disease management, 196
  - risk factors, 193–196
  - subcortical and cortical Lewy bodies, 192
  - and vascular dementia, 324
- Depression, 115, 215
  - antidepressant, 51, 53
  - assessment of, 50
  - definition, 49
  - and falls, 50–51, 53
  - mechanism of
    - behavioural, 51–52
    - neuromuscular, 52
    - pathological, 52
    - through symptoms, 53
  - prevalence and risk factors, 49, 50
- Derived functional gait assessment scale, 335

- Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV), 50
- Diffusion tensor imaging (DTI), 176
- Digit Span Forward and Backward, 294
- Digit Symbol scores, 59
- Digit Symbol Substitution Test scores, 59
- Digoxin, 157
- Direct cortical stimulation, 123
- Dismobility
  - age effect on, 24, 25
  - definition of, 22
  - interpreting gait speed, 22
  - mobility disability, 23
  - mobility measurement, 22, 23
  - multisystem causes of, 22, 23
  - slow gait speed, 24
- Donepezil, 15, 16, 157, 197
- Dopamine agonists, 200
- Dopamine transporter (DAT), 175
- Dopaminergic and cholinergic neurotransmitter functions, 327
- Dopaminergic loss, 174
- Dopaminergic therapy or DBS, 196
- Droxidopa, 197, 332
- Dual-task (DT) training, 374, 378
  - assessment strategy, 366
  - clinical mobility tests, 358
  - cognition-related mechanisms for falls, 364
  - cognitive impairment, 343, 344, 363
  - cognitive sub-performances, 365
  - cognitive tasks, 358
  - comprehensive inclusion criteria, 345
  - comprehensiveness, 346, 365
  - data analysis for fall reduction, 363
  - description, 361
  - divided attention, 365
  - document potential prioritization, 361
  - duration of intervention, 363
  - effects on falls, 360
  - exercise control activity, 362
  - fall assessment, 359
  - fall prevention program, 344, 358
  - fall prevention training, 362
  - formal search strategy, 344
  - identified articles, characteristics, 347–352, 354–357
  - inclusion criterion, 365
  - innovative training strategies, 366
  - interactive training system, 358
  - interventions, 367
  - limitations, 367
  - mobility assessments, 364
  - motor status, 359
  - motor task with walking, 358
  - motor tasks, 358
  - motor training, 366
  - multi-component fall prevention programs, 344
  - multi-component studies, 360, 367
  - objective electronical measures, 358
  - open search strategy, 344
  - physical training domain in fall prevention research, 364
  - quality criteria, 346
  - quality rating, 360, 361, 365
  - quality scoring system, 365
  - review criteria, 367
  - search strategy, 344
  - short physical performance battery, 358
  - single-component fall prevention programs, 344
  - single-component design, 360, 367
  - timed-up-and-go, 358
  - training programs, 344
  - undersampling, 363
- Dual-task gait assessment, 97, 98
- Dual-task gait paradigm, 8, 59
- Dynamic gait index, 335, 381
- E**
- Electromyography sensors, 404
- Embedded home sensors, 201
- Enalapril, 154, 157
- Ergonomical solutions, 403
- European fall related projects, 417
- Evidence-based interventions for falls prevention
  - falls in hospitals, 250, 251
    - delirium prevention and mobility, 252, 255
  - environment, 252, 253
  - exercise, 251
  - falls risk assessment, 251, 253
  - knowledge, 254
  - medication, 252
  - multifactorial interventions, 254
  - NICE quality statements, 251
  - service model change, 254
- falls risk factors, 245, 246
  - hospitalized older people, 246
  - in nursing homes, 246
- in nursing homes, 245, 247–250
  - exercise, 247, 248
  - medication review, 248
  - multifactorial interventions, 250
  - multiple interventions, 250
  - psychological interventions, 249

- social environment, 249
  - vitamin D supplementation, 249
- EXBELT program, 237, 238
- Executive dysfunction, 5
- Executive functions (EF), 8, 17, 53, 58, 59, 115–117, 276, 290, 291, 293, 294, 297, 302, 310
- Exercise, 218, 247, 251
  - effect on falls, 248
  - in older adults with cognitive impairment
    - cognitive function and falls, 274, 275
    - falls prevention, 279, 280
    - falls risk factors, 275–277
    - mechanisms, falls reduction, 280–282
    - neural underpinnings, 277–279
    - therapeutic interventions, 200, 201
- Exercise-associated fall prevention strategies, 345
- Exercise-based studies, 367
- Exergame-based training, 366
- Exoskeletons, 403
  
- F**
- Fall prediction
  - body/postural sway, 416
  - gait assessment, 416
  - near falls, 416, 417
- Fall preventions, 310, 312, 319, 367
- Fall-related injuries, 4, 100, 140, 141
  - in older adults, 43
  - serious fall-related injuries, 44
- Fall risk factors, 402
- Fall risk increasing drugs (FRIDs), 38, 159
- Falls, definition of, 35, 87, 110
- Falls Efficacy Scale (FES), 55, 381
- Falls Efficacy Scale – International (FES-I), 216, 302
- Falls prevention, 310, 312, 319, 367
  - assessment of cognition, 269, 270
  - clinical practice guidelines, 263–266
    - ABS/BGS screening algorithm, 265
    - AGS/BGS guidelines, 266
  - fall risk screening and assessment, 264
  - gaps in, 270
  - in older adults, 266, 267
  - MMSE, 264, 265
  - RR/OR, 266
  - evidence-based interventions for (*see* Evidence-based interventions for falls prevention)
- Falls reduction, DT trials quality, 366
- Faraday's law of electrical current induction, 383
- FARSEEING work packages (WP), 418
- Fear of falling (FoF), 44, 45, 111, 112
  - assessment, 54, 55
  - definition, 54
  - prevalence and risk factors, 54
  - with risk of falls, 55–57
- First-line rehabilitation strategy, 139
- 5-HT6 receptor inhibitor idalopirdine, 335
- Five-item Geriatric Anxiety Inventory, 100
- Five-times-sit-to-stand test (FTSS), 98, 269
- Fixed priority training (FPT), 293
- Fludrocortisone, 217
- Fluoro-deoxy-D-glucose (FDG)-PET, 178
- fMRI, *see* Functional magnetic resonance imaging (fMRI)
- fNIRS, *see* Functional near-infrared spectroscopy (fNIRS)
- Fractional anisotropy, 176, 177
- Frailty, 71, 77, 78
  - and cognition
    - association, 72, 73
    - and falls, 75, 76
    - possible mechanism, 73, 74
  - definition of, 67
  - with dementia and fallers, 76
  - measurements, 67–69
  - mechanism of
    - animal models, 72
    - hallmarks of ageing, 71, 72
    - telomeres, 72
    - theory, 69, 70
  - outcomes and quality of life improvement, 76, 77
- Frailty index (FI), 68, 69
- Freezing, 196
- Freezing of gait (FOG), 119, 120, 123, 381, 417
- Freezing of gait (FOG)-Questionnaire (FOG-Q), 197
- Frontal gait, 214
- Frontal temporal dementia (FTD), 118
- Fronto-executive network (FEN), 278
- Fronto-parietal network (FPN), 278
- FTSS, *see* Five-times-sit-to-stand test (FTSS)
- Functional magnetic resonance imaging (fMRI), 172, 294, 295
- Functional near-infrared spectroscopy (fNIRS), 172, 173, 291, 301
  
- G**
- Gait and balance impairment, 214, 310
- Gait and mobility impairments, 145
- Gait assessment, 17

Gait dynamics, 109  
 Gait hypokinesia and freezing, 332  
 Gait quality, 141  
 Gait slowing and high stride time variability, 42  
 Gait variability, 42, 56  
 Gait variability and fall risk in older adults  
   brain imaging correlates, 120, 121  
   clinical conditions and falls  
     cardiovascular conditions, 113, 114  
     depression, 115  
     executive and memory functions, 115–117  
     frontal temporal dementia (FTD), 118  
     mild cognitive impairment and Alzheimer's disease, 117, 118  
     neurodegenerative disease, 117  
     Parkinson's disease, 118–120  
     peripheral neuropathy, 114, 115  
     post-stroke, 114  
   cognitive interventions, 123  
   genotypes, 121  
   intervention modalities, combinations of, 124, 125  
   normal aging, 110  
     age-associated changes in multiple physiologic systems, 111  
     body stability, 112  
     childhood to adulthood, 110  
     in elderly individuals, 110  
     FoF, 111, 112  
     index of walking performance, 107, 108  
     intra-individual variability, 111  
     low variability, 110  
     medial-lateral trunk instability, 111  
     obstacle negotiation, and falls, 113  
     quantifying, 108, 109  
     sex and falls, 113  
   pharmacological interventions, 123, 124  
   physical interventions, 123  
   rehabilitation strategies, 121  
   stride-to-stride gait variability, 122  
 Gait velocity, 290  
 Galantamine, 16  
 Galvanic skin response sensors, 404  
 Geriatric Depression Scale (GDS), 50  
 Geriatric giants, 3, 158, 160  
 Geriatric syndromes, 4–6, 24  
 Global cognition, 57, 58  
 Global cognitive functioning, 99  
 Go/No-Go Test, 277

Grey matter atrophy, 168  
 Grey tsunami, 151  
 Guideline- and theory-based multicomponent intervention, 237  
 Gyroscopes, 201

## H

Hawthorn Effect, 363  
 Health consequences of reduced mobility  
   clinical consequences, 24, 26  
   physiological and psychological consequences, 26, 27  
   public health action, 27  
   reduced mobility, 26  
 Hemispheric asymmetry reduction of old age (HAROLD), 171  
 Heterogeneity, 67  
 High gait variability, 5  
 High-definition transcranial direct current stimulation (HD-tDCS), 377  
 High-level-care nursing homes, 247  
 Hip strategy, 7  
 History of falling, 38  
 Holy grail approach, 4  
 Hospital Elder Life Program (HELP), 231, 255  
 Hospital mobility programs, 255  
 Human gait, 107, 405  
 Human movement related activities, 415  
 Hypometabolism, 57  
 Hypoperfusion, 178

## I

Idiopathic Parkinson's disease, 191  
 Impaired gait and balance, 275, 281  
 Impaired mobility, 75  
 Individualized assessment, 236  
 Inertial measurement units (IMUs), 404, 415  
 Inertial measurement units-based database, 418  
 Inertial measurement units-based fall detection algorithms, 412  
 Inhibitory choice stepping reaction time task (iCSRT), 59  
 Intact executive functioning, 276  
 Intelligence quotient (IQ), 29  
 Intensive Care Delirium Screening Checklist, 233  
 Interhemispheric inhibition (IHI), 386  
 Internet of Things (IoT), 419  
 Intracortical facilitation (ICF), 385

**L**

- Left dorsolateral prefrontal cortex (DLPFC), 295
- Levodopa, 192, 196, 197, 217
- Levothyroxine, 152
- Locomotor and sensory systems, 326
- Long interval intracortical inhibition (LICI), 385
- Long-term depression (LTD)-like effect, 387
- Lower-level gait disorders, 95

**M**

- Machine learning (ML) algorithms, 414, 415
- Magnetic resonance imaging (MRI), 168, 170
- MCI, *see* Mild cognitive impairment (MCI)
- MDS-UPDRS, 194
- Mean diffusivity, 177
- Mechanical devices, 403
- Medication debridement, 161
- Methylphenidate, 16, 17, 199
- Microelectromechanical systems, 408
- Midodrine, 217
- Mild cognitive impairment (MCI), 5, 36, 41, 192, 274–277, 282, 324, 419
  - amnesic vs. non-amnesic forms, 212
  - clinical assessment, 215–217
  - falls management, 217, 218, 221
  - gait variability and fall risk in older adults, 117, 118
  - non-pharmacological interventions, 219–220
  - risk factor, 212–215
- Mild parkinsonian signs, 214
- Mini-BESTest, 335
- Mini-Cog, 160
- Mini-Mental State Examination (MMSE), 4, 35, 39, 57, 160, 180, 195, 196, 264, 265, 267, 269
- Mobility aids, 139, 140, 147
  - and cognitive aspects, 143–147
  - and falls, 140
    - adverse biomechanical consequences, 142
    - cane users, 142
    - dichotomous response, 140
    - elevated falls risk, 141
    - fall-related injuries, 140
    - gait quality improvement, 141
    - for maintaining balance and adapting walking, 141
    - risk of falls, 140, 142
    - for safety of older adults, 142
    - single cane, 141
    - walkers, 139, 142

- Mobility disability, 23, 139
- Monoamine-deficiency theory, 52
- Montreal Cognitive Assessment (MoCA), 99, 160
- Morse Falls Scale, 251, 253
- Motor and cognitive performances, 343
- Motor and sensory impairments, 310
- Motor-cognitive training, 297, 302
- Motor-evoked potential (MEP), 384
- Motor freezing behaviors, 328
- Motor signs, 214
- Motoric cognitive risk syndrome (MCR), 212
- Multi-Dimensional Dementia Assessment Scale, 36
- Multi-domain training of cognition, 298, 300, 301
- Multi-factorial interventions, 311
- Multiple system atrophy (MSA), 191
- Muscle atrophy, 55
- Music therapy, 217

**N**

- National Institute of Clinical Excellence (NICE), 250, 251
- Neural noise, 290
- Neurobiology of falls, 166
  - assessment of falls, 179
  - cognitive and biomechanical characteristics, 179
  - demographics, 181
  - neuroimaging, 167
    - age-related CNS structure, markers of, 168–170
    - application, 167
    - AV-1541, 178
    - Blood Oxygen Level Dependent (BOLD) response, 171–174
    - fractional anisotropy, 176, 177
    - mean diffusivity, 177
    - metabolism, 178
    - perfusion, 177
    - PET, 174, 175
  - nigrostriatal dopaminergic system, 166
  - in PD, 327
  - sample size and source, 180–181
  - study design, 181–182
- Neurodegeneration, 5, 278
- Neurodegenerative disease, 117

- Neuroimaging, 167, 277, 294, 295  
 age-related CNS molecular characteristics,  
   measures of, 174, 175  
 age-related CNS structure, markers of,  
   168–170  
 application, 167  
 AV-1541, 178  
 blood oxygen level dependent (BOLD)  
   response, 171, 172  
   fMRI, 172  
   fNIRS, 172, 173  
   neural activation and falls, measures of,  
     173, 174  
 of metabolism, 178  
 micro-structural characteristics, markers of  
   fractional anisotropy, 176, 177  
   mean diffusivity, 177  
 of perfusion, 177  
 Neuroplasticity, 302, 303  
 Neuropsychiatric disorders, 100  
 Neurotransmitter depletion, 290  
 Neurotransmitters, 16  
 New prescription medications, 38  
 NICE, *see* National Institute of Clinical  
   Excellence (NICE)  
 Nicotinic receptor subtype-specific  
   compounds, 336  
 Nigrostriatal dopaminergic denervation, 325  
 Nigrostriatal dopaminergic system, 166  
 Non-fatal fall injury, 211  
 Noninvasive brain stimulation, 202, 374, 377,  
   380, 381, 391, 392  
 Noradrenergic drugs and mobility in PD, 332  
 Normal pressure hydrocephalus (NPH), 191
- O**
- Old-generation intervention programs, 237  
 Optimal mobility, 273  
 Orthogeriatric model of care, 254  
 Orthostatic hypotension, 217, 280  
 Osteoporosis, 199–200  
 Otago Exercise Program (OEP), 274
- P**
- Paired-pulse TMS protocols, 385, 386  
 Paracetamol, 154  
 Parkinson's disease (PD), 37, 41, 97, 117,  
   174, 175, 191, 215, 277, 297, 324,  
   325, 417  
   cholinergic studies, 335  
   controlled noradrenergic clinical trials, 333  
   DBS and non-invasive stimulation,  
     201, 202  
   dopaminergic deficits, 192  
   fallers, 328, 330  
   falls prevention, approaches to, 200  
   functional neuroanatomy and  
     neurochemistry, 202  
   gait variability and fall risk in older adults,  
     118–120  
   idiopathic, 191  
   noradrenergic drugs and mobility, 332  
   optimizing disease management, 196  
     cognitive strategies, 199, 200  
     medical management, 196, 197  
     surgical management, 197–199  
   postural instability and gait difficulties,  
     330  
   risk factors, 193–196  
   subcortical and cortical Lewy bodies, 192  
   therapeutic interventions  
     environmental assessment and  
       modification, 201  
     exercise/physiotherapy, 200, 201  
     new devices in fall prevention, 201  
 Parkinson's disease dementia (PDD), 37, 41  
 Parkinsonian gait, 214  
 Parkinsonism  
   definition of, 191  
   non-motor symptoms, 191  
 Patient Health Questionnaire (PHQ), 50  
 Pedunculo pontine nucleus (PPN), 16, 166,  
   198, 325  
 Performance Oriented Mobility Assessment,  
   358  
 Peripheral neuropathy, 95, 114, 115  
 Personalized medicine approach, 336  
 Phenothiazines, 280  
 Physical restraints, 234–238  
 Physical therapy (PT), 311, 407  
 Physics of frailty, 70  
 Physiological Profile Assessment (PPA), 173  
 Polypharmacy, 151, 213, 218  
 Positron emission tomography (PET), 174,  
   175, 294  
 Post-fall syndrome, 55  
 Postural instability (PI), 196, 202, 330  
 Postural-instability and gait-difficulty (PIGD),  
   119, 195, 330  
 Posture first strategies, 8, 291  
 Posture second strategy, 8  
 Potentially inappropriate medications (PIMs)  
   Beers' criteria, 156  
   START, 156  
   STOPP, 156  
   STOPPFRAIL criteria, 156  
 Pregabalin, 157  
 Prescribing cascade

- definition, 157
  - examples of, 157
  - Presynaptic cholinergic signaling, 336
  - Primarily automatic motor task, 5
  - Primary motor sensory network (SMN), 278
  - Progressive supranuclear palsy (PSP), 8, 191
  - Prosthetics, 403
  - Pseudodementia, 53
  - Psycho-active drugs and falls in elderly, 327
  - Psychomotor retardation, 230
  - Psychotropic drugs, 214
  - Public health efforts, 334
- Q**
- Quantitative spatio-temporal gait parameters, 5
- R**
- Rasagiline, 197
  - Rate of falls, 245
  - Raven's progressive matrices, 294
  - Reactive postural response, 276
  - Recent hospitalization, 38
  - Recruitment process, 346
  - Rehabilitation strategies, 121
  - Remote monitoring
    - big data, 419, 420
    - innovation, 420
    - IoT functionality, 419
    - patients during walking, 405
    - socio-economical barriers, 407
    - validation, 420
  - Repetitive transcranial magnetic stimulation (rTMS), 202, 387
    - causal pathway to falls, 390, 391
    - cognition in older adults, 389, 390
    - gait and postural control in older adults, 388, 389
  - Restraint use
    - definition, 234, 235
    - epidemiology, 234
    - reasons and consequences of, 235, 236
    - restraint reduction, 236–238
  - Rivastigmine, 16, 17
  - Rowland Universal Dementia Assessment Scale, 160
- S**
- Sarcopenia, 21, 23–24, 213
  - Screening Tool of Older Person's Prescriptions (STOPP), 156
  - Screening Tool to Alert doctors to Right Treatment (START) criteria, 156
  - Selegiline, 197
  - Self-awareness for physical ability, 59, 60
  - Sensory motor, 290
  - Sertraline, 154
  - Service model interventions, 249
  - Short interval intracortical inhibition (SICI), 385, 388
  - Short-latency afferent inhibition (SAI), 386
  - Short physical performance battery (SPPB), 172
  - Single photon emission computed tomography (SPECT), 177
  - Single-pulse TMS paradigms, 385, 386
  - 6 minute walk test, 269
  - Sleep disorders, 53
  - Slow gait speed, 24
  - Smartphones, 414
  - Socio-economic impact of falls, 45
  - Spinal and supraspinal neuromuscular reflex arcs, 373
  - Stepping strategy, 7
  - Sternberg task (transfer task), 295
  - Stimweaver™, 381
  - STOPPFRAIL criteria, 156
  - Strength-balance-cognitive (SBC) training, 13
  - Striatal dopamine binding, partial dopaminergic mechanism, 332
  - Stride length variability, 118
  - Stride time variability, 16, 290
  - Stride-to-stride variability, 16, 92
  - Stroop Color Word Test, 276
  - Subcortical cholinergic denervation, 325
  - Substantia nigra pars reticulata (SNr), 199
  - Survey of Activities and Fear of Falling in the Elderly (SAFFE), 55
  - Syncopal loss of consciousness, 100
- T**
- Tai Chi exercise, 200, 218, 279
  - tDCS, *see* Transcranial direct current stimulation (tDCS)
  - Telomeres, 72
  - Test-to-test reliability of gait variability, 109
  - Theta-burst stimulation (TBS), 385
  - Thought-provoking brief report, 324
  - Threshold-based fall detection algorithms, 413–414
  - Timed-Up-and-Go test (TUG), 269, 297, 298, 335, 381
  - Tinetti balance score, 196, 269
  - Tissue/bone regeneration, 403
  - Trail-Making Test A (TMT-A), 58, 277
  - Transcranial alternating current stimulation (tACS), 377



- Transcranial direct current stimulation (tDCS),  
120, 202, 376, 377, 382
- Transcranial Doppler (TCD), 177
- Transcranial electrical stimulation (tES)  
on causal pathway to falls, 382, 383  
clinical research, 374  
on cognition in older adults, 381, 382  
gait and postural control, 378, 380, 381,  
383  
sham protocols, 375  
stroke rehabilitation, 380  
therapeutic strategy, 374  
types, 375–377
- Transcranial magnetic stimulation (TMS), 123  
action potentials, 383  
biological aging, 387  
brain functionality, 384  
cortical excitability, 384  
cortical physiology related to falls in aging  
and disease, 387  
electromagnetic induction,  
principle of, 383  
forms of, 374  
gait and postural control, 388  
noninvasive brain stimulation  
technique, 383  
types  
paired-pulse TMS, 385, 386  
rTMS, 387  
single-pulse TMS, 385
- Transcranial magnetic stimulation-derived  
markers of cortical activity, 388
- Transcranial magnetic stimulation-evoked  
potential (TEP), 384
- Transcranial magnetic stimulation-induced  
electrical currents, 383
- Transcranial magnetic stimulation-induced  
TEPs/MEP, 384
- Transcranial random noise stimulation  
(tRNS), 377
- Transfer effects, 289, 293–295, 303
- Treadmill training enhanced with virtual  
reality (TTVR), 13
- TUG, *see* Timed-Up-and-Go test (TUG)
- U**
- Unified Parkinson's disease Rating Scale  
scores, 330
- Usual gait speed, 25, 290
- V**
- Variable priority training (VPT), 293
- Vascular dementia, 16, 324, 382
- Vascular depression, 52
- Vascular parkinsonism (VaP), 191, 192
- Venlafaxine, 154
- Ventrolateral prefrontal cortex (VLPFC) post  
training, 295
- Video recording, 410, 411
- Virtual reality (VR), 419  
for falls reduction, 313, 314, 318, 319  
motor-cognitive training, 311, 312  
VR-based interventions on falls in older  
adults, 315–317
- Visual searching and anticipatory postural  
adjustments, 56
- Vitamin D, 53, 124, 200, 217, 247, 249,  
252, 357
- Voice response time (VRT) task, 143–145
- W**
- Wearables, 408  
inertial measurement unit, 408–410  
inertial sensors, 408  
sensors and gait, 405–408
- White matter hyperintensities (WMH), 168,  
170, 176